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THE CONSERVATIVE TREATMENT OF OCCLUSIVE ARTERIAL DISEASE*

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DURING the last ten years, great advances have been made in the conservative treatment of occlusive arterial disease. Major amputation in the course of the routine care of thromboangiitis obliterans has, as a result of conscientious efforts on the part of many workers throughout the country, become a rather rare occurrence. In 100 consecutive cases treated by the Vascular Clinic of the New York Post-Graduate Medical School and Hospital, major amputations were performed in only 3 cases, and figures similar to these have emanated from several sources. This is in contrast to major amputations in 50 to 70 per cent of cases prior to the use of the newer methods. We have been engaged in attempting to determine how much could be accomplished in the way of saving extremities by intensive conservative therapy. It is probable that some of these patients might have been somewhat better off financially and that their periods of disability might have been shortened by amputation earlier in the course of treatment. It is my belief, however, after studying these cases, that this figure would probably not be higher than 10 per cent. Moreover, amputation is considered the easiest course; it requires no courage, and very little can be learned from it. Conclusions that have resulted from conscientious, painstaking care of the difficult cases have often been applied with great success in the care of the less advanced lesions.

The problems associated with arteriosclerosis obliterans are more difficult. As has been pointed out previously,[1] this is one of the greatest economic, social and medical questions confronting the American people. There are roughly 25,000,000 people over the age of fifty in the United States today. This number is rapidly increasing, owing to the age shift in the population. Of these persons, 60 per cent, or 15,000,000, will die of cardiovascular disease, for the most part associated with arteriosclerosis obliterans affecting the vessels of the heart, brain, kidney and other parts of the body. By contrast, only 9 per cent will die of cancer. Yet the endowments for cancer and the facilities for research in that very dramatic field have been far in excess of those available for the study of the heart and blood vessels. In spite of this neglect, material that has inconspicuously been accumulated has resulted in a better understanding of the physiologic pathology involved and has laid a sound groundwork for a more intelligent approach to the problem of treatment. The marked diminution in the amputation rate and the greater percentage of restoration in walking ability in cases of intermittent claudication have been somewhat in excess of anticipation. To date, however, this has not resulted in such satisfactory results as those obtained in the treatment of thromboangiitis obliterans.

Although there are more than fifty recognized vascular diseases and syndromes, each disease and, in fact, each patient should be studied on the basis of the exact status of the circulation of the patient. Certain forms of therapy are especially helpful in the treatment of the major occlusive arterial diseases, thromboangiitis obliterans and arteriosclerosis obliterans. I propose to discuss the conservative aspect of these forms of treatment very briefly.

Rest

One of the most important factors in the treatment of any patient with ulceration or gangrene is rest. This should be used intelligently and on the basis of sound physiology. If the extremity is elevated, it easily becomes ischemic, and a tendency toward gangrene results. If it is kept dependent, the blood flow toward the heart be-

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comes more difficult, and congestion, with a relative ischemia, may arise. Reid[2] has shown that the correct level is the point at which the tip of the extremity is from 7 to 15 cm. (3 to 6 inches) below the level of the heart. At this level, gravity assists the flow of arterial blood into the limb, and the blood is not retarded in its return by too greatly increased venous back pressure. Rest should be continued until the lesion is healed, except in the specific vascular exercises enumerated below.

Active Vascular Exercises

Buerger[3] has described vascular exercises that, since they are in wide use today, do not necessitate an elaborate description of the original suggestions. I should like to propose, however, the following modification, which applies to these exercises and is on a more sound physiologic basis than that generally applied. The physician should first elevate the patient's extremity until pallor develops. The length of time necessary for this to occur should be noted. He should then lower the extremity until rubor develops and, again, should measure the time necessary for this change. These times should be given to the patient as indicating the exact periods for elevation and dependency, rather than arbitrary units of time. From time to time in the course of treatment, these reactions should be rechecked, and the indicated changes in instructions to the patient should be given.

Allen[4] has suggested a modification of Buerger's exercises in which the foot is extended downward and raised by flexion of the ankle joint; the toes are turned inward and then outward, and are then separated and closed. This is helpful, if it is not too painful.

Care of the Extremities

Meticulous care of the skin and nails of extremities that are suffering from impaired circulation is of vital necessity. Hands or feet that have not yet developed ulceration or gangrene should be bathed daily, and the skin and nails kept soft by the subsequent application of lanolin, olive oil or other substances having a similar effect. Nails and calluses must be pared with great care, since a very large percentage of ulcers are precipitated as a result of minute injuries that would normally heal promptly. The use of strong dekeratinizers, such as salicylic acid (in high percentage), is not to be recommended; if they are used for stubborn calluses, the situation must be kept under careful observation.

Frequent examinations should be made for evidence of epidermophytosis, since the cracks produced by this condition are frequent portals of entry for very serious secondary bacterial invaders. In my experience, soaks for potassium permanganate in dilutions of 1:7000 to 1:10,000 for thirty minutes every two or three days are usually a satisfactory method of controlling this fungus. It is advisable, however, to continue these soaks at weekly intervals long after the fungus has apparently disappeared. Gentian violet in a 5 per cent aqueous solution may be used, but the stronger antiseptics and fungicides are distinctly contraindicated, since the condition of the tissues is frequently such that more harm than good results.

When ulceration occurs, the problem immediately becomes more serious and emergent. This fact is too often not recognized or acted on by the physician. There is a dictum in our clinic: It is far better surgery to take meticulous care of a minute lesion than it is to perform a major amputation in the amphitheater. The cutting away of the involved area before the available circulation has been adequately improved usually results in a larger ulceration, with an unfavorable result. Efforts, such as those subsequently outlined in this paper, should be made to improve the blood supply, since that is the primary problem. Soaks should be used. All strong antiseptics, such as iodine and the mercurials, should be avoided: they frequently do more harm to the delicate new endothelial buds and new cells than to the infecting organisms. Gradually, by careful daily dissection, sloughs and other debris should be removed, thus allowing the endothelial, epithelial and connective-tissue cells to extend in from the edges. It is essential to make certain that purulent material is not accumulating under the scabs, which often appear healthy and innocuous. Lifting of the edges frequently reveals pus that is eroding and undermining the tissues covered by and surrounding the scab. It is imperative to maintain adequate drainage by removing or cutting windows in the scab; this should be followed immediately by a saline soak.

If the situation results in gangrene of digits or of an entire hand or foot, careful observation should be routine for evidence of rapid extension of infection, such as lymphangitis or a septic syndrome. When this occurs, amputation may be necessary. When, however, the gangrene is slowly extending, time should be allowed for self-amputation whenever possible, since the circulation is usually then adequate for healing at the point of separation. One can help this along by keeping the point of separation clean and by cutting per-

sisting tendons and other fibrous tissue a little at a time. Finally, the digit may be lifted off with little or no discomfort and without a local anesthetic, which is apt to be harmful because of the pressure produced in the tissues. Adrenalin in an anesthetic is especially contraindicated, since it produces vasoconstriction; I have seen cases in which massive gangrene was precipitated by this substance. If the tip of a phalanx protrudes beyond the level of the separation, it will probably be necessary to remove it down to that level on the shaft of the bone. This may be accomplished slowly, in small fragments, by the use of a scalpel — after which healing will tend to take place more satisfactorily. After each dressing, a thirty-minute soak in sterile physiologic saline solution at a temperature of 96°F. helps to ensure drainage and cleanliness, following which the area is dried sterilely and kept under dry thermostatically controlled heat, as described elsewhere.

Nerve sections are occasionally used on our service if we are unable to control the pain in any other way, but judging by the results in other clinics as well as those in our own, we are inclined to believe that too frequently the claims of complete relief represent wishful thinking on the part of the surgeon and a disregard of the pain and especially the paresthesias of which the patients complain when permitted to voice their woes. Similar complaints of very annoying paresthesias frequently follow the use of alcohol block of the lumbosacral sympathetic nerves, and surgeons who have never noted such results should spend more time listening to their patients. Nevertheless, one is sometimes obliged to use these measures in an endeavor to bring all possible collateral circulation into play before the gangrene becomes widespread.

A discussion of the surgical technics that are indicated when conservative therapy fails and that require the finest judgment is not within the scope of this paper. It is most important that, when amputation is to be performed, the correct level be determined on the basis of adequate circulation for healing by careful clinical study. In doubtful cases, tests such as oscillometric readings, arteriograms, histaminase-flare reactions, and vasodilatation tests prove useful.

Abstinence from Tobacco

It hardly seems necessary to elaborate on the need for total and permanent abstinence from tobacco in the care of occlusive arterial disease, since great volumes of experimental evidence confirm the studies of Maddock and Coller,[5] Barker,[6] Wright and Moffat[7] and Lampson.[8] Thromboangiitis obliterans appears to be more specifically aggravated by smoking than arteriosclerosis obliterans,[9-11] but in the latter disease it is essential to realize that, whereas the major vessels may be occluded, the small collateral branches (on which the life of the tissues depends) are subject to spasm. If the blood supply has been reduced by disease to the bare minimum necessary for the life of the tissues, it is disastrous to produce repeated spasm in these small vessels and thus reduce the blood supply to a point incompatible with the life of the tissues. For further investigation on this subject, one may find a review of the points involved in a recent symposium[11] on vascular disease. Clinical experience has shown that if a physician wishes to obtain good results in the treatment of either of these conditions he must impress his patient with the fact that his outlook depends on conformity to the edict, "No smoking, now and forever."

Alcohol

As a more cheerful and compensatory form of treatment, the use of alcohol may be prescribed. Alcohol has been demonstrated to be a marked vasodilator, and it is also of considerable value as a sedative. We therefore recommend the liberal use of alcohol almost to the point of inebriation during the acute, painful periods of ulceration or gangrene, and its moderate daily use after the lesions have healed and the patient has again become active. It is our experience that patients rarely object to this form of therapy.

Baths

Various types of baths have been used. We formerly used contrast baths, but there are several reasons why these have been largely abandoned in our clinic. In the first place, the best containers reach only to the knees, and too often the area of blockage is well above that level, so that the changes in the metabolic demands caused by the baths cannot be adequately compensated for by the vessels. Secondly, when already damaged vessels are forced into sudden vasospasm, they may remain closed, thus complicating the picture. Thirdly, many patients complain of the severe pain that occurs during the cold phase. In place of these, we use a modification of the sitz bath, in which the patient sits in a tub containing at least 30 cm. (12 inches) of water at a temperature of 34 to 38°C. (95 to 100°F.) for thirty minutes once a day. This tends to produce vasodilatation of the patient's vessels from the hips down, and is a very satisfactory form of therapy except that it is not recommended when open lesions are present.

Soaks

In the place of wet dressings, which have largely been abandoned, because unless watched with rare acuity they become cold and chill the small endothelial buds into inactivity, we have used soaks, two or three times daily, for fifteen to thirty minutes. We use a boric acid solution or a physiologic solution of sodium chloride at 36 to 38°C. (96 to 100°F.). Great care should be taken to keep the temperature within these limits. After each soak, the foot is carefully dried and placed under a thermostatically controlled cradle, thus preventing chilling and at the same time allowing for softening of the crusts and adequate drainage.

Heat

It is probable that the use of local heat has done far more harm than good in the treatment of peripheral vascular disease. I have seen more than 50 cases in which severe ulceration, massive necrosis or gangrene was primarily produced by the extensive use of diathermy or short-wave, infrared or other forms of local heat applied to an area where there was a marked arterial impairment resulting from peripheral vascular disease. When intensive heat is used locally in the presence of marked impairment of the circulation, greatly increased metabolic demands cannot be met, since insufficient blood is available. Furthermore, intensive heat cannot be carried away, so that the tissue rapidly becomes broiled, almost as if it were a piece of meat. I have seen cases in which holes produced by burning, with subsequent necrosis, extended through the flesh of the patients' feet until finally the bones of the feet were exposed. Seven of these patients have lost their legs, and 2 have died. It is therefore vital to use only controlled heat, with the temperature between 31 and 36°C. (88 and 96°F.), depending on the needs of the patient. This can best be accomplished by means of a thermostatically controlled light.

Reflex heat, on the other hand, is of great value.[12] The application of warm pads, short-wave currents, diathermy and so forth to various portions of the body not involved results in a tendency toward reflex vasodilatation of the major vessels and their collaterals distally. It has definite advantages and, so far as we know, is without danger. Wilkins, Doupe and Newman[13] have shown that the increase in blood flow resulting from local heat is not so great as that produced by warming the body.

Typhoid Vaccine

The intravenous use of typhoid vaccine has been proved to be of great value in the treatment of thromboangiitis obliterans, although we do not recommend its use in cases of arteriosclerosis obliterans. Specially prepared typhoid vaccine should be used. The H antigen prepared by Eli Lilly and Company and recommended by Barker[14] is satisfactory. For some years, we have used typhoid vaccine prepared by the Kirk Biological Laboratories, of Bloomfield, New Jersey. For this purpose, it is diluted to a strength of 100,000,000 organisms per cubic centimeter. It is given intravenously, and the first dose should not exceed 5,000,000 organisms. The object is to produce a fever of 2 or 3°F., *without a chill*. When the repeated dose fails to produce an adequate response, the amount should be increased by 3,000,000 to 5,000,000 organisms. This should be given every three or four days, and a careful temperature chart should be kept.

Administration of this vaccine is continued until the ulceration or gangrene is healed, and for several months thereafter for the purpose of developing adequate collateral vessels. In our experience, the use of typhoid vaccine produces a more rapid response both in release from pain and in healing than the intravenous use of hypertonic saline, citrate or similar solutions.

Vasodilating Drugs

In general, the use of the vasodilating drugs has been rather disappointing in the treatment of occlusive vascular disease. They may be roughly divided as follows: the nitrites and allied compounds; theobromine, Theocalcine and allied compounds; the choline compounds[15]; and papaverine. Although each of these products has specific indications and values in other fields, in the treatment of these two major vascular diseases, they are of rather doubtful merit. For example, in studies published several years ago,[16] it was shown that reflex heat was much more reliable and effective than papaverine.

Tissue Extracts

The therapeutic use of various tissue extracts has been studied in our laboratory for ten years. We have employed various extracts prepared from the heart, skeletal muscles, liver and pancreas. Of these, the pancreatic tissue extracts have seemed the most effective in the treatment of intermittent claudication in man. Details of these studies have been reported elsewhere.[17] In brief, however, it is our opinion that the present, relatively pure form

of pancreatic extract (Depropanex) does favorably affect intermittent claudication. Ergometric studies that demonstrate this fact rather clearly have been made.[17] Patients have been enabled to walk longer distances after changing from previous therapy through the single addition of pancreatic tissue extract. More than 200 patients with this syndrome have been studied, slightly over 60 per cent showing a marked improvement and another 15 per cent showing moderate improvement — marked improvement was taken to mean an increase in walking ability whereby a patient who could walk only two or three blocks was finally able to walk ten blocks or more. This, we believe, enables him to carry on most types of occupation in a conservative manner.

This material is injected in doses of 3 cc. intragluteally two or three times a week. It has been established that pancreatic extract is nontoxic when given intravenously, although it is not used by this route in the treatment of intermittent claudication. The exact mechanisms of its action are not very well understood. It is an epinephrine antagonist in rabbits, but has not been shown to have marked vasodilating properties in man. The most popular theory at present is that it acts as a replacement product, supplying a greater concentration in the blood of substances that are essential to correct muscle metabolism but have been reaching the muscle tissue in reduced amounts because of the narrowing of the total vascular bed. Early studies of the effects of pancreatic extracts on the development of atherosclerosis in rabbits fed on cholesterol appeared to indicate that they retarded the deposition of cholesterol in the wall of the aorta. Further studies with additional series of rabbits have, however, failed to confirm this observation.[18] Further fractionation of this substance is now being attempted in the hope of isolating an active principle.

Mechanical Therapy

Mechanical therapy in various forms has become the vogue rather recently. One of the first of these machines to receive general attention was that known as the pressure-suction boot. Although this principle was used in the treatment of the circulation before 1800, it remained for Landis and Gibbon[19] and Herrmann and Reid[20] to perfect mechanized units for this purpose. Since the apparatus has had much widespread publicity and general use, it is not necessary for me to go into the details of the technic. As in most new forms of therapy, the experimental claims were overoptimistic. It was at various times stated to be of value in the treatment of arteriosclerosis, thromboangiitis obliterans, Raynaud's syndrome, acute embolism, frostbite and almost every form of circulatory impairment that comes to mind. Actual experience with this apparatus has markedly reduced the indications for its use. At present, it may be said to be of value in the treatment of frostbite, acute embolism (if a well-trained surgical and medical team is not available for the surgical removal of the embolus) and a few selected cases of arteriosclerosis obliterans in which the lesion is small and not infected and the level of blockage is below the level at which the cuff is applied. On the other hand, the following contraindications have been definitely established: the presence of thrombophlebitis — this excludes many cases of thromboangiitis obliterans, since these patients tend to develop thrombophlebitis very easily; the presence of infection in the lesion; and lesions whose level is higher than that at which the cuff can be applied.

Reactive Hyperemia and Intermittent Venous Occlusion

The use of intermittent venous occlusion has been advocated from several sources. Most of this work is based on the original studies of Lewis and Grant,[21] in which reactive hyperemia, both arterial and venous, was described. We have conscientiously used this apparatus on 23 cases at the New York Post-Graduate Medical School and Hospital. Favorable reports have been published by Collens and Wilensky,[22] de Takats, Hick and Coulter,[23] and Wilson and Ogston.[24] Unfavorable results have been published by Veal and McCord[25] and Allen and McKechnie,[26] and we[27] have also reported unfavorably on the use of this equipment. The reactive hyperemia that undoubtedly occurs is, as pointed out by Roy and Brown[28] and Lewis and Grant,[21] in the final analysis an attempt on the part of the tissues deprived of a proper blood supply to become repossessed of it, and the phenomenon of reactive hyperemia is related in its degree to one factor, namely, the blood-flow debt, which is usually a product of the amount by which flow is reduced and the time over which the reduction has been maintained. We question very strongly the advisability of subjecting these already malnourished tissues to additional periods of deprivation of adequate blood supply to increase the blood flow thereafter, especially when the amount of the blood flow is roughly equal to that developed during the preceding phase of the cycle. We have, therefore, discontinued the use of this form of therapy in our clinic, although — as in all types of treatment — there

are reports of patients who apparently improved while this therapy was being carried on.

Vasoscillating Bed

The third form of mechanical therapy that has been receiving widespread attention is that known as the vasoscillating bed, which was first described by Sanders.[29] By means of this bed, the head and feet of the patient are alternately elevated and lowered, a complete cycle taking from one to three minutes. This is another form of Buerger's exercises, the great difference being that this type may be continued for twenty-four hours a day if necessary, whereas Buerger's exercises can be maintained only for twenty minutes once or twice a day. We do not find it necessary to use this or any other elaborate mechanism in the treatment of thromboangiitis obliterans, but in the treatment of arteriosclerosis obliterans with impending or actual gangrene or ulceration we have found this to be of great value. More than 150 cases have now been studied at our hospital. Although it is difficult in all forms of therapy to evaluate the results satisfactorily, we have become increasingly convinced of its merit. Our experience conforms with the results recently published from the Mayo Clinic[30] and the Vascular Clinic of the Northwestern Medical School.[31] Healing of ulcerations that had previously been extremely obstinate and a general improvement in circulation in many cases have been noted. The progress is relatively slow, and it is frequently necessary to keep the patient on the bed steadily for at least a month. After this time, the patient may be allowed to be up and about during the day, but it is imperative for him to have eight hours' treatment at night on the bed. This is continued over a period of months or even years, and it appears to be of real value in increasing the ability of the collateral vessels to take over the burden of the functions associated with tissue nutrition. We usually employ a thermostatically controlled light as part of the equipment with the bed.

* * *

Of all types of experimental or clinical research, none presents more difficulties than the correct evaluation of therapeutic agents. Many published studies are valueless because the author has neglected to consider other factors that he introduced into the picture simultaneously with the form of treatment that he was attempting to evaluate. Other studies are open to grave question because both known and unknown factors that affect the results were unavoidably present.

A proper estimation of the worth of a new treatment, therefore, rests on its use only in the presence of adequate controls and freedom from extraneous factors that may be influencing the clinical course of the patient. For example, forms of therapy have been reported as being of great value in the treatment of peripheral vascular diseases when they have been employed at the same time that the patient was put at complete rest, made to abstain from smoking, given soaks and wet dressings and allowed to take alcohol by mouth. Any or all of these factors are capable of markedly influencing the therapeutic response. In addition, the factor of seasonal variation is frequently neglected. Vascular diseases (with the exception of erythromelalgia) usually tend to respond favorably to warm weather, so that if, for example, cases of Raynaud's syndrome or thromboangiitis obliterans are treated, the factor of environmental temperature trend may play a role in the picture.

Failure to consider these factors has frequently necessitated a complete revision of the original conceptions of the value of a therapeutic agent. This paper has been presented with careful consideration of this aspect of the problem, but I should like to emphasize the fact that even under these conditions it is highly probable that further reevaluation will take place during the next ten years.

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A POSTOPERATIVE FOLLOW-UP STUDY OF FOUR HUNDRED AND SIXTY-NINE THYROCARDIAC PATIENTS*

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IN 1934, a follow-up study of 303 thyrocardiac patients was reported from this clinic.[1] Those cases had been observed after subtotal thyroidectomy over a period of one to ten years. Excellent results and a low operative mortality were demonstrated. The present report concerns a further follow-up study of the same group, and in addition, the present state of 166 cases in which operation was performed from January, 1932, to January, 1937.

TABLE 1. *Miscellaneous Clinical Data as Recorded in 469 Thyrocardiac Patients.*

CLINICAL FINDING		NO. OF CASES
Mitral stenosis, exclusive of cases with a rheumatic history and apical systolic murmurs		27
Aortic regurgitation (rheumatic)		2
Aortic stenosis (rheumatic)		1
Active rheumatic fever, with partial auriculoventricular block		2
Syphilitic aortitis		1
Patent ductus arteriosus		1
Adhesive pericarditis (?)		1
Pericarditis		1
Interventricular block		3
Regular rhythm	1	
Auricular fibrillation	2	
Auricular flutter		2
Paroxysmal tachycardia		2
Coronary disease		2
Coronary disease, with auricular fibrillation		2
Cardiac asthma		2
Pulsus alternans		1
Asthmatic bronchitis		3
Severe anemia		2
Postoperative angina		9
Hypertension (160/90, basal, or greater)*		71
Preoperative	35	
Present since operation	36	
Diabetes at or since operation		15
Postoperative myxedema		14
Transient	7	
Permanent	7	

*Includes only the 166 cases in the second group.

The definition of the term "thyrocardiac" given in the previous report is as follows: a patient with hyperthyroidism who has persistent auricular fibrillation or flutter up to the time of operation, or congestive heart failure with or without regular heart rhythm or both. Data concerning associated findings are given in Table 1.

It is not the purpose of this report to discuss in detail the pathologic physiology of the heart in hyperthyroidism. A review of this subject has recently been made from this clinic.[2] We wish to point out again, however, the fundamental difference between congestive heart failure due to hyperthyroidism on the one hand and congestive heart failure from intrinsic heart disease on the other. The heart fails in the former because of its inability to maintain circulatory needs for increased bodily metabolism, and in the latter because it cannot maintain circulatory needs for a normal bodily metabolism. The superimposition of auricular fibrillation in either group greatly adds to the heart's inefficiency. These relations are diagrammatically presented in Figure 1.

FIRST GROUP (1922–1932)

The majority of these patients were seen in the clinic during the five-year period following operation. Thereafter, contact was made mostly by questionnaires, which were frequently completed by the patient's physician. In 1932, the final out-

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come was determined in 84 per cent, whereas in 1938 and 1939, 83 per cent were followed (Table 2).

Mortality

In 1934, the case mortality following operation was reported as 4.3 per cent.[1] Since that time, 13 of this group of patients have been reoperated on, with 2 deaths, the total mortality following operation being 5.0 per cent.

formed elsewhere before the patients came under our observation. Thus, the probable operative mortality is about 3 per cent.

Sufficient time has not yet elapsed, nor has the number of cases been large enough, to permit the construction of accurate tables of life expectancy. However, a presentation of certain facts demonstrates the outcome to the present time. If the number of years that the patients were expected to live are totaled, the average for those who died after having survived operation is seventeen years. Actually, these patients lived only an average of six years; only 1 patient lived out his life expectancy. Of the total now living, only 6 have lived beyond their expected term of life, and the rest have still not reached their predicted span of life. Figure 2 shows the average expectancy of each year group up to and including 1928, and the number of years actually lived to date. These fall short of life expectancy, and it is doubtful if the group living at present will make up the discrepancy.

Figure 3 shows the present status of these patients. The numbers now alive, dead and untraced are easily seen. Since 1926, the majority are still living, but before that time the majority were dead. It probably may be assumed that the same proportion of those alive and dead exists among the untraced patients. Figure 4 shows what is known about patients who could not be

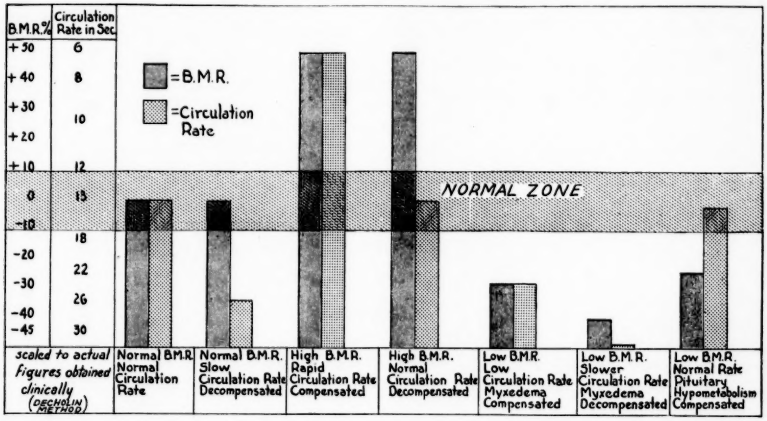

FIGURE 1. *Relation of Circulation Rate to Metabolic Rate in Various Types of Thyroid Disease and Hypometabolism.*

The data are based on clinical observations of circulation times (arm-to-mouth method, with decholin) and basal metabolic rates. The thyrocardiac patient with congestive failure is represented in the fourth column, with elevated basal metabolic rate and normal circulation time; this should be compared with the findings for the patient with ordinary congestive failure (second column).

TABLE 2. *Follow-Up Data on Patients in the First Group.*

DATA	FOLLOW-UP IN 1933*	FOLLOW-UP IN 1939†
Number of cases operated on	303	303
Number of cases traced	256	252
Number of patients living	208	164
Number of patients living who had congestive heart failure		104
Number of patients dead (including operative deaths)	48	88
Number of patients living, with regular heart rhythm	149	122
Number of patients living, with auricular fibrillation	56 (27%)	42 (25%)
Subsequent reoperation because of recurrent hyperthyroidism and congestive failure (2 operative deaths)		2

*One to ten years.
†Six to sixteen years.

A little more than five hundred operative procedures were carried out on these 303 patients, including an estimated nineteen operations per-

traced at this time. It depicts the number of patients lost track of during any year following operation and the number of patients followed for twelve or more years until last heard from, and also the number who lived for various intervals following operation.

Persistent or Recurrent Hyperthyroidism

Up to the time of this follow-up, hyperthyroidism recurred in 27 cases at various intervals

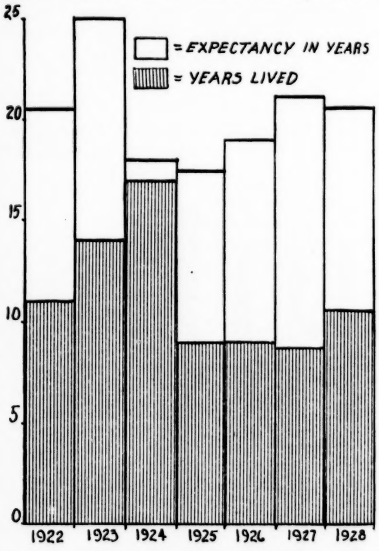

FIGURE 2. *The Average Expectancy in Years and Average Years Lived by Thyrocardiac Patients.*

The number of years lived to date is shown in the cross-hatched areas, and falls short, by half, of the natural expectancy. The small number of cases in each group does not permit accurate conclusions, but the trend is distinctly abnormal.

following operation. It is not always possible to decide whether a patient has persistent or recurrent hyperthyroidism, but of these, 6 might be said to have had persistent hyperthyroidism; the remainder had recurrent hyperthyroidism. Recurrence developed as long as ten years after operation. Of the 14 who were reoperated on, 3 died postoperatively (1 included in the former mortality figures), and 10 have so far remained well, or were well until they died; in 1, the disease has persisted and the patient is still taking Lugol's solution. Five patients were given x-ray treatment; 4 are still well, and 1 has not been traced. Six patients were well controlled on Lugol's solution; 4 were not, and they were given roentgen-ray treatment as mentioned above. Of the total group, 6 are dead, 3 untraced, and 6 alive.

To determine the percentage of recurrent or persistent hyperthyroidism following subtotal thyroidectomy is at best a difficult problem. Many factors are involved, such as adequate or inadequate surgery, the length of time followed, the accuracy of the initial diagnosis, the type of goiter and the method of computing the percentage. To say that a certain number of patients have recurrences within a five-year period does not mean that the chance of recurrence is ended. Considered from the point of view of the whole life history of these patients, the final estimate of recurrence cannot be made until that history is complete.

Of the 303 patients operated on in this group, 41 have had to have secondary operations or other methods of controlling hyperthyroidism up to the present time. Nineteen of the 41 were operated on before they were first seen in the clinic. It is true that some of these patients may have had inadequate surgery, especially since the operations were done between 1917 and 1925; nevertheless, they must be included.

If these 19 cases, as well as the postoperative deaths and 51 untraced cases, are excluded, there remains a total of 221 cases from which the percentage of recurrences can be computed. Hyperthyroidism developed in 22, making a percentage of 10. In the 221 cases, 71 patients have died since operation. Of those dead, 4 were known to have hyperthyroidism (2 postoperatively); there is thus a known recurrence in 18 of 154 living patients, or 12 per cent for this particular group of patients with hyperthyroidism. The final percentage of recurrence cannot be accurately foretold, therefore, until these 154 patients have all died, which may require another ten years or more of observation.

This experience with recurrent or persistent hyperthyroidism, along with consideration of the 19 patients who had been operated on before coming under our care and who fell into the thyrocardiac group because of either insufficient surgery or a persistent or recurrent hyperthyroidism, illustrates that serious consequences may occur if patients are allowed to drift along with what seems to be mild hyperthyroidism. If the disease is mild, some may be controlled with iodine, but they must be followed carefully and operated on again if necessary. It seems probable that 2 patients who died postoperatively from recurrent hy-

perthyroidism could have been saved had they submitted to operation before severe heart failure and moderately severe hyperthyroidism developed. The degree of hyperthyroidism does not always foretell whether fibrillation or heart failure will subsequently develop. The diminished cardiac reserve in many of these cases, because of degenerative or other types of heart disease, cannot withstand at times even the burden of mild degrees of thyroid overactivity without loss of compensation.

Auricular Fibrillation

In the original group, there were 262 cases of fibrillation. Quinidine was used in 64 cases and was successful in restoring normal heart rhythm in 52. At the 1932 follow-up, there existed 56 cases of persistent auricular fibrillation. At the present writing, 42 cases probably exist. In 5 cases in which the heart rhythm had been restored to normal, auricular fibrillation again developed without a known recurrence of hyperthyroidism, whereas 4 other patients returned with auricular fibrillation caused by recurrence of hyperthyroidism. Recurrence of auricular fibrillation took place in 2 cases with the administration of thyroid for mild postoperative myxedema, but normal rhythm was quickly restored—in one by the use of quinidine and in the other spontaneously after the withdrawal of thyroid. The presence of auricular fibrillation after operation did not appear to shorten life as judged by the fact that 27 per cent of the patients alive in 1932 and 25 per cent of those alive in 1938 had auricular fibrillation. Most of these patients are taking daily rations of digitalis.

Recurrence of congestive heart failure is rare in the absence of coexistent organic heart disease, such as mitral stenosis. It developed a second time in 4 cases, owing to recurrence of hyperthyroidism.

Causes of Subsequent Deaths

Twelve patients were said to have died of heart disease; 11 died from either cerebral hemorrhage or embolus when auricular fibrillation was present. It is difficult to assign the cause of these deaths accurately, but embolus seems the likeliest possibility. One patient died of mesenteric embolism. Four died of cancer, and in many the cause was not determined.

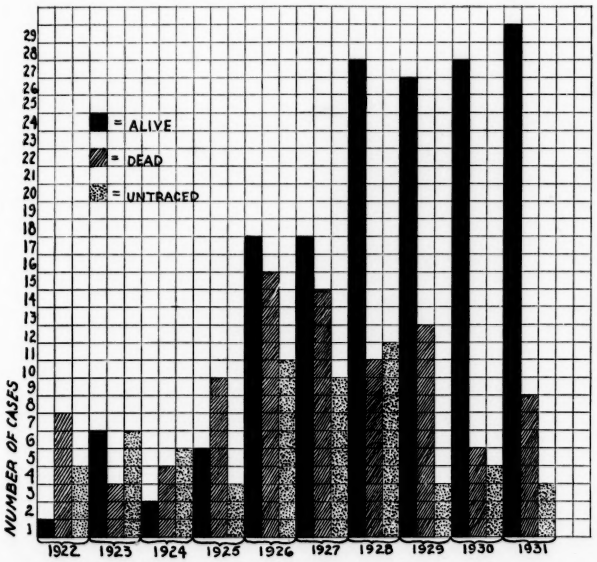

FIGURE 3. *The Number of Living, Dead and Untraced Patients in Each Year Group.*

Present Condition of Health

An attempt to grade results is at best difficult and is not entirely satisfactory. Infirmities of age

and the presence of some unrelated disease, along with our inability to examine a good many of the patients personally, are some of the reasons why an accurate statement regarding results at the time of follow-up is impossible.

In 111 cases, the rhythm is regular, and the patients are in good health; in 33, auricular fibrillation is present, but the patients are otherwise in good health; and in 20, the patients are in poor health from diverse causes, either auricular fibrillation or regular rhythm being present.

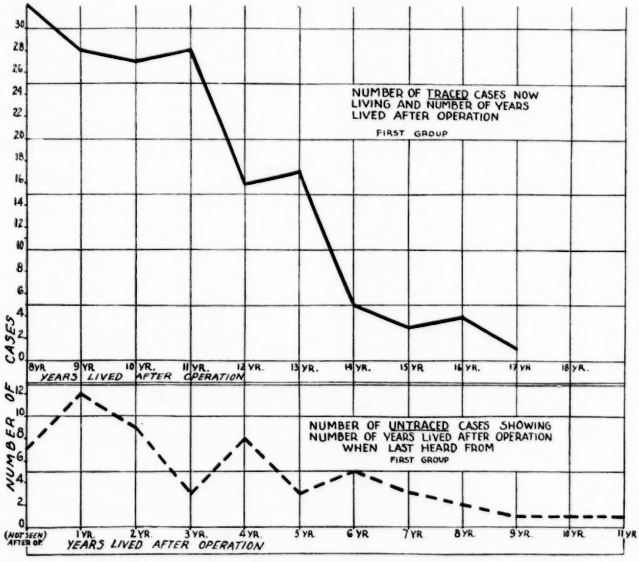
NUMBER OF TRACED CASES NOW LIVING AND NUMBER OF YEARS LIVED AFTER OPERATION
FIRST GROUP
NUMBER OF CASES
YEARS LIVED AFTER OPERATION
NUMBER OF UNTRACED CASES SHOWING NUMBER OF YEARS LIVED AFTER OPERATION WHEN LAST HEARD FROM
FIRST GROUP
(NOT SEEN) AFTER OP
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FIGURE 4. *Data on Survival of Traced and Untraced Patients. Although the number of patients operated on in 1922, 1923 and 1924 was relatively small, the trend drops sharply after eleven years.*

SECOND GROUP (1932–1937)

The recent group of 171 thyrocardiac cases (1932–1937) is summarized in Table 3. One fact stands out in comparison to the first group, namely, that the number of cases of congestive heart failure seems to have decreased in relation to the number of cases of established auricular fibrillation. A little more than a third in this group had definite congestive failure as compared with more than half of those reported in the first group. The probable explanation is that these cases are being recognized or that the patients are being advised to have operation earlier than formerly.

Mortality

The case mortality in this group was 4.7 per cent. For the two groups, a total of 469 cases, the case mortality from operation is 4.5 per cent.

Fifty-four one-stage operations, 94 two-stage operations, and 17 three-stage procedures (two hemithyroidectomies and a pole ligation) were carried out; this makes a total of 293 operative procedures and thus gives an operative mortality of 2.7 per cent.

Persistent or Recurrent Hyperthyroidism

Four of the 166 patients operated on had had a previous thyroidectomy. In 5 of these cases, hyperthyroidism recurred; 3 patients were reoperated on, and 2 are taking Lugol's solution. The incidence of recurrence to date in these cases is low, but sufficient time has not elapsed to permit a comparison with the first group.

Auricular Fibrillation

Twenty-four per cent of those traced and alive still have auricular fibrillation, as compared with 25 per cent in the first group. Quinidine sulfate was used in 33 cases, and in 20, normal rhythm developed during its administration. In some cases

in which quinidine fails to restore normal rhythm shortly after operation, a spontaneous return to normal may occur at a later date. Four such cases were noted in this group. On the other hand, in our earlier experience, normal rhythm was not infrequently restored in patients who had persisted in having auricular fibrillation two and three years after operation.

TABLE 3. *Data on Thyrocardiac Cases Admitted from 1932 to 1937.*

DATA	NUMBER OF CASES					
	1932	1933	1934	1935	1936	TOTAL
Total	40	25	36	35	35	171
Operated on	37	25	35	34	35	166
Auricular fibrillation	36	23	34	33	34	160
Auricular fibrillation with congestive heart failure	10	6	12	8	15	51
Normal rhythm with congestive heart failure	4	2	2	2	1	11
Operative deaths	0	2	1	3	2	8
Subsequent deaths	5	4	2	2	1	14
Survivals	25	15	30	27	31	128
Untraced	7	4	2	2	1	16
Normal rhythm at present						98
Auricular fibrillation at present	6	6	1	5	12	30
Recurrent hyperthyroidism	2		1	2	0	5
Myxedema	3	1	0	0	2	6
Reoperations	1		1	1		3

Basal Metabolism

A comparison of the basal metabolic rates before and three months after operation is given in Figure 5. These include all cases of persistent hyperthyroidism or myxedema occurring at three months. As can be seen, the largest number of cases before operation had a metabolic rate between +30 and +40 per cent, and after operation a rate of between +10 and −10 per cent.

SUMMARY

Four hundred and sixty-nine thyrocardiac cases in which operation was performed from 1922 to 1937 have been followed. In the first group of 303 patients operated on between 1922 and 1932, 164, or 54.1 per cent, are living; 122 have normal heart rhythm, and 42 continue to have auricular fibrillation. Of the second group of 166 operated cases, 128 patients are still living, 98 of whom have normal heart rhythm.

The case mortality was 4.5 per cent, and the operative mortality was slightly less than 3.0 per cent.

The incidence of recurrent hyperthyroidism in the first group followed from six to sixteen years was over 10 per cent, which shows that the incidence increases the longer the period after operation.

Although these patients are restored to normal activity for the most part, their expectancy of life based on the present follow-up falls considerably short of the predicted expectancy.

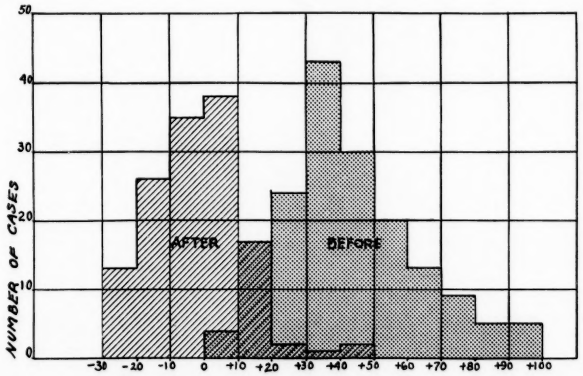

FIGURE 5. *Basal Metabolic Rates before and Three Months after Operation.*

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POLLEN DISEASE IN THE ABSENCE OF POSITIVE SKIN TESTS*

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THERE is a small but distinct group of patients who, with the advent of the spring, summer or fall, suffer from characteristic bronchial, nasal or ocular symptoms, reminiscent of pollen disease, but who on skin testing fail to react to any of the prevailing pollens and molds.[1-5]

That these symptoms are due to some atmospheric inhalant, most probably pollens, is suggested by the fact that they recur each year, during a well-defined pollen period, and cease when this period is over. In addition, the intensity of the symptoms varies directly with the extent of pollen pollution in the air.

In further support of this hypothesis is the fact that when patients in this group are placed in air-filtered rooms, or when they change residence to a new locality with a different pollen flora, they are relieved. Most important, however, is the observation that these patients respond satisfactorily to specific pollen therapy, and in some cases even systemic reactions occur in the course of treatment. Such therapeutic results and the concomitant systemic reactions are possible only when patients are specifically sensitive to the substances injected.

What these patients lack to fulfill the criteria of pollen disease is positive skin tests. In some cases, this lack seems only relative, since suggestive endermal reactions may be obtained with pollen extracts in high concentration; high-potency extracts, however, often produce false positives, thus minimizing the value of the tests. In others, the more delicate ophthalmic[6] or nasal[7] tests, performed with dry, unaltered pollens, may give a clue to the correct diagnosis. But even these tests bear no constant relation to the symptoms. The only rational approach to this problem seems to be the history of the case, backed by a knowledge of the prevailing atmospheric flora during the respective seasons of the year, and a proper appraisal of the presenting symptoms.

The presenting symptoms in this group merit particular mention. In patients with bronchial complaints, wheezing may be absent or slight, the chief difficulty being either a harassing cough or complete apnea. Many patients become refractory to adrenalin and fall into a state of complete physical exhaustion bordering on collapse.

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Those suffering from nasal symptoms complain more of stuffiness than of sneezing, and their chief difficulties are constant blowing of the nose and a sense of suffocation, particularly at night. The so-called "ocular" group suffer from severe itch, altogether out of proportion to the local conjunctivitis. In general, severity characterizes the symptomatology in this group.

The incidence of negative skin tests to pollen has been variously estimated at between 2[1] and 13 per cent[2] of the total cases of hay fever.

During the last few years, I have observed 28 such patients, or about 7 per cent of the total pollen cases treated. Eleven of these, or 39 per cent, suffered from asthma, and a similar number from hay fever. Three, or 11 per cent, had cough as the chief complaint, and 3 others had conjunctivitis.

An evaluation of the clinical characteristics of allergy in this group reveals an incidence of positive family history, past history of allergy and blood eosinophilia comparable with similar findings in other types of human hypersensitiveness (Table 1). In the absence of positive skin tests, the results of the more delicate ophthalmic and nasal tests are recorded.

TABLE 1. *Findings in 28 Allergic Patients with Negative Skin Tests.*

FINDING	NO. OF CASES	PER CENT
Family history of allergy	19	68
Past history of allergy	7	29
Blood eosinophilia		5 (average)
Positive ophthalmic tests	22	78
Positive nasal tests	4	14

Contrary to what might be expected in this group, the incidence of positive ophthalmic tests was higher than that of nasal tests when performed with dry pollens. This close relation between the ocular mucosa and the shock organ merits further investigation.

Nineteen of these patients, — 12 with asthma, 6 with hay fever and 1 with cough, — who were followed for a year or longer and who received the benefit of close supervision and treatment, were the subjects of the present report. There were 9 males and 10 females, with an average age of thirty-seven years. The average age at the onset of symptoms was thirty years, which is somewhat higher than the expected average in frank hay fever.

In practically all cases, the symptoms extended over more than one pollen season: 9 patients complained of symptoms in spring, summer and fall; 6 in summer and fall; 3 in spring and summer; and 1 in spring and fall. This, again, is unlike the events in frank pollen disease, in which a single pollen sensitivity generally prevails. Evidently, aside from the fact that skin tests show these patients to be refractory, as a group they have other characteristics as well.

The management of these cases and the selection of pollens for treatment present a definite problem. In the absence of positive skin tests as a guide, one must draw chiefly on the history of the case and on experience with allergic patients whose skin tests are positive. On this basis, patients having symptoms during May and early June were considered sensitive to tree pollens, of which oak and birch are most important. Lesser offenders among the trees, such as elm, poplar, ash, hickory and others, were omitted from consideration because the periods of pollination are short, the dates overlapping in many cases, and because the amounts of pollen shed are comparatively small.

Patients suffering from early June to the middle of July were considered sensitive to grass pollens, and those having fall symptoms, from the middle of August to October, were designated as ragweed cases.

Other atmospheric offenders that prevail during the various pollen seasons and must be reckoned with are molds, particularly Alternaria, Hormodendrum and Aspergillus. Since the exact dates of their pollution in the air are not well defined, and in the absence of positive skin tests, their etiologic significance could not be determined.

Pollen dosage presents another problem for consideration. Most of these patients can tolerate large doses without any untoward reactions. Others, however, may have systemic reactions even from a small dose. Therefore, caution rather than experience is required in selecting the proper dose for the individual patient. Contrary to the procedure followed in frank pollen disease, — in which treatment is initiated with comparatively high dilutions and the doses are increased by 0.05 or 0.10 cc., — in the nonreacting pollen group, the technic is somewhat different. The following is presented as a working basis, which, however, must be flexible in conformity with the individual needs of the patient:

Initial dose	0.1 cc. of a 1:500 dilution
Second dose	0.1 cc. of a 1:100 dilution
Third dose	0.1 cc. of a 1:30 dilution
Fourth dose	0.1 cc. of a 1:20 extract.

All further increases are made from the 1:20 extract until an arbitrary final dose of 1.0 cc. is reached.

Throughout the treatment, watch must be kept over possible systemic reactions; when these occur, the need of a more gradual increase in dosage and of a possible smaller final dose becomes apparent.

Since in the earlier cases a 1:10 pollen extract was used, for which the equally potent 1:20 extract was later substituted, all pollen doses were for convenience calculated on a 1:10 scale.

Table 2 is descriptive of the symptomatology, type of pollens, number of doses, the size of maximum dose and the results of therapy in each case.

TABLE 2. *Therapy and End Results in 19 Treated Patients.*

CASE NO.	SYMPTOM	POLLENS	MAXIMUM DOSE (1:10)	TOTAL NO. OF DOSES	RESULTS
			cc.		
1	Asthma	Tree and grass	0.20	20	Good
2	Asthma	Tree and grass	0.75	21	Good
3	Cough	Grass and ragweed	0.65	22	Good
4	Asthma	Tree, grass and ragweed	0.40	24	Good
5	Hay fever	Tree, grass and ragweed	0.70	27	Good
6	Asthma	Tree, grass and ragweed	0.60	27	Good
7	Asthma	Grass and ragweed	0.85	29	Good
8	Asthma	Tree and ragweed	0.60	31	Good
		Averages	0.59	25	
9	Hay fever	Grass and ragweed	0.10	18	Fair
10	Hay fever	Grass and ragweed	0.50	20	Fair
11	Hay fever	Tree, grass and ragweed	0.70	27	Fair
12	Asthma	Tree, grass and ragweed	0.90	31	Fair
13	Hay fever	Tree, grass and ragweed	0.60	32	Fair
14	Asthma	Tree, grass and ragweed	0.45	35	Fair
15	Asthma	Tree, grass and ragweed	0.75	36	Fair
		Averages	0.57	28	
16	Asthma	Tree and grass	0.30	10	Poor
17	Hay fever	Tree, grass and ragweed	0.80	13	Poor
18	Asthma	Grass and ragweed	1.00	27	Poor
19	Asthma	Grass and ragweed	0.20	28	Poor
		Averages	0.45	20	

In addition, the average size and number of doses for patients with good, fair and poor results from treatment are included at the bottom of the respective columns. The estimation of end results in pollen therapy on the scale of good, fair or poor has been adopted because of its simplicity and fair amount of accuracy.

Table 2 shows further that patients with good and fair results received a higher average number of pollen doses and larger final doses than patients with poor results. This suggests a possible causal relation between the intensity of treatment and the end results. At the same time, patients who failed to obtain satisfactory results had a higher incidence of systemic reactions than those whose responses to therapy were more favorable (Table 3). These figures suggest that patients with poor results have a higher degree of "shock organ" sensitivity, and that with some modification in the

technic, improvement in this group may not be impossible.

Altogether, 15 of the 19 patients, or 79 per cent, were benefited by the treatment. These figures are impressive and emphasize the merits of pollen therapy in patients whose skin tests are negative.

TABLE 3. *Results of Treatment in Relation to Systemic Reactions.*

Result of Treatment	No. of Cases	Systemic Reactions	
		No. of cases	per cent
Good	8	2	25
Fair	7	1	14
Poor	4	2	50

Discussion

The group as a whole is presented to illustrate a type of allergy that is masked by a lack of positive skin tests. However, the clinical characteristics of these patients — their symptomatology, their aptitude for allergy, their response to specific therapy and, finally, their tendency to systemic reactions from an overdose of pollen extract — leave no doubt that their etiologic grouping is correct.

The important factor in this group is the seasonal incidence of the disease. The general tendency would be to place such patients among the undiagnosed or intrinsic cases whose symptoms are due to causes from within the body, but the proper appraisal of the disease opens an approach to specific therapy that promises some degree of success.

An example of such success is the patient in Case 2, whose seasonal asthma confined her to her bed each spring for a period of from six to eight weeks, but who has remained well with specific treatment; another example is the patient in Case 5, who was similarly affected each summer, but who has lost no time from work since treatment began. In Case 7, the patient collapsed and was in a state of unconsciousness in July, 1939, because of severe asthma, and was saved only through heroic treatment with adrenalin, an oxygen tent and so forth. In 1940, under pollen therapy, he had two mild attacks, which required no adrenalin. In these three cases, nasal and ocular tests to the offending pollens were negative.

The occurrence of clinical symptoms from the inhalation of small quantities of pollen in the air, in spite of negative ophthalmic or nasal tests, defies explanation.

Of particular interest is Case 3; for twenty years, the patient had had an intractable summer cough, lasting from the middle of June until the fall. Skin tests were negative, and ophthalmic tests doubtful. Treatment with extract of timothy and ragweed brought complete relief. In this case, cough was the presenting symptom, and pollens were the cause.

The occurrence of so many constitutional reactions (in 6 out of 19 patients) seems inexcusable, except that in the past, I have vainly attempted to treat similar patients with smaller doses. It was only in desperation that stronger doses were used, and only on the assumption that when skin tests are negative, the tolerance for pollen is high. In a measure, this is true, but it is also true that the shock organs, particularly the bronchi, have their own measure of tolerance, regardless of the response of the skin. The question then arises, What can be done to avoid such reactions? No definite answer can be suggested except the cautious increase of each successive pollen dose as treatment progresses. The local reactions to the injections in this group were few, often delayed in onset, and occurred only with doses close to 1.0 cc. of the extract. But even in these cases, the local reactions bore no relation to the systemic reactions, most of which occurred in the absence of local reactions.

Another point that merits discussion is the number of doses injected in each patient. Many of those in dilutions higher than 1:500 were undoubtedly superfluous. Yet, it is possible that the summation of the repeated injections ultimately bore results. Thus, in treating these patients, one may omit the lower dilutions, and safely start with a 1:500 extract. Beyond this, the advances must be cautious, and experience alone must be the guide in estimating further doses.

No explanation can be offered for the failures, particularly in those patients who experienced constitutional reactions. Evidently, the pollens used were specifically indicated, the dosage was carried to the point of tolerance and even higher, and yet the results were poor. The only consoling thought is that failures also occur in skin-sensitive patients, in spite of the most intensive treatment; however, in the skin-negative group the percentage of failures was higher.

In the final analysis, the mechanism of relief in pollen therapy is not clear, although the discovery of the blocking antibody in the serum of treated patients offers some ground for speculative thought.[8] Pollen therapy is justifiable chief-

ly on the basis of so many excellent clinical results. By the same token, it seems reasonable to treat the refractory group with pollen extracts if the history points to pollen disease. The broader application of these observations must find its way to the large number of patients with perennial allergy, who, in the absence of positive skin tests and lacking the seasonal element, present a difficult problem both in diagnosis and in treatment.

Summary and Conclusions

Pollen disease in the absence of positive skin tests presents a definite problem in diagnosis and treatment.

A knowledge of the atmospheric flora in a given locality and of the dates of pollination makes a correct diagnosis possible.

Treatment given with corresponding pollen extracts offers relief in a high percentage of cases.

The technic of treatment is outlined, and the incidental systemic reactions are pointed out as possible complications.

Several characteristics of patients with negative skin tests are described, and emphasis is placed on the severity of their symptoms.

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NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTIETH ANNIVERSARY

May 13 and 14, 1941

Tuesday, May 13

THE scientific session of the New Hampshire Medical Society was opened at the Hotel Carpenter, Manchester, at two-thirty o'clock in the afternoon, with President Ezra A. Jones presiding.

Three papers dealing with fractures were presented, as follows: "Fractures of the Forearm and Humerus," Dr. Augustus Thorndike, Jr., Boston; and "Femoral Fractures," Dr. George W. Van Gorder, Boston; and "Fractures of the Foot and Ankle," Dr. Otto J. Hermann, Boston. This was concluded by a talk, "Glaucoma," by Dr. Paul A. Chandler, Boston.

Wednesday, May 14

The morning session convened at eleven o'clock, with President Jones presiding.

The following remarks were made by the visiting delegates from other New England state medical societies:

Dr. Frank R. Ober, Boston: It is a pleasure to be here with you, and I bring the best wishes of the Massachusetts Medical Society to the New Hampshire Medical Society.

I am going to say only a word, which has to do with postgraduate teaching. A few years ago, the Massachusetts Medical Society established the New England Postgraduate Assembly, for the benefit of all doctors in New England; your state, Maine, Vermont and Rhode Island voted to join the assembly, and last year Connecticut came in. Incidentally, Connecticut has conducted a clinical congress for a great many years — I think next year will be the sixteenth. I know of only one other state — Kansas — that has had meetings of this type for a longer period.

The program committee represents the hospitals and medical schools of Boston, the different states and the members of the assembly. The speakers are from outside Boston, and are chosen because they are outstanding in their fields of medicine.

The next meeting will be held on October 29 and 30. Last year, we had it in the middle of November, and it rained cats and dogs for the two days; the year before, it rained cats and dogs the first day. This year we hope for better weather.

We charge a fee that is supposed to cover the general expenses and those of getting the speakers; last year, however, we lost over $600.

The meetings are held in Cambridge, at the Sanders Theatre, in Memorial Hall, Harvard University. We believe the assembly should be an entirely scientific affair; hence, there are no exhibits of any sort.

I hope that all of you will act as spark plugs in your district or county societies, and urge as many members to come to the next meeting in October as possible.

Dr. William T. Rowe, Rumford, Maine: The Maine Medical Association sends hearty greetings to the New Hampshire Medical Society at its one hundred and fiftieth annual meeting, and best wishes for a successful gathering.

You are, indeed, fortunate to be able to secure for your meetings some of the leaders of the medical world. Last year, as the Maine delegate, I had the pleasure of listening

to the president of the American Medical Association here in this auditorium, and today I hope to have the added pleasure of listening to the new president of the American Medical Association, Dr. Frank H. Lahey, of Boston.

The annual session of the Maine Medical Association will be held at the Marshall House, York Harbor, on June 22, 23 and 24. On Sunday evening, we are planning to have a guest speaker who has recently returned from England. Monday and Tuesday mornings, the system of conferences will be continued. Monday and Tuesday afternoons, there will be guest speakers from outside Maine. Monday evening, there will be a reception in honor of the President of the Association and his wife, Dr. and Mrs. Thomas A. Foster.

The Maine Medical Association congratulates you on your long and honorable record. We invite you all to be with us at York Harbor at our annual meeting.

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Dr. Arthur B. Landry, Hartford, Connecticut: I bring you greetings and best wishes from the Connecticut State Medical Society on this, your one hundred and fiftieth anniversary. You may celebrate your past rightfully, because it has been a notable and a dramatic one, full of achievements.

I congratulate you, and all the more do I congratulate you because inherent in your past is the urge and vision that must regard this celebration as only a pause and a breathing spell, before you gain further momentum for the unfulfilled account that lies before you.

It is, alas, true that many celebrations of the past become deadly, nursing complacency and anesthetizing fresh endeavor and conflict. Henry Ward Beecher tells the story of the dog that, in its puppyhood, chased a squirrel up a tree until he came to a hole in the tree, and that he spent the rest of his natural life barking up the hole of this tree. But that is not true of the members of this society, and certainly it is not true of the medical profession as a whole.

In these times there are many changes that demand intelligence and generous tolerance. Never was the opportunity so great for advance, service and achievement. If there ever was a time to follow St. Paul's challenge in our profession it is now; we should forget the things that are beyond and reach forward to those before us. So, let us press on toward the mark of our high calling.

We, of the State of Connecticut, will celebrate our one hundred and fiftieth anniversary next year, in Middletown, where the first meeting of the Connecticut State Medical Society was held. We invite you all to come and see us at that time, and we assure you of a very warm welcome.

Dr. Arthur H. Ruggles, Providence, Rhode Island: To this most auspicious and historical occasion, I bring greetings and very best wishes from the Rhode Island Medical Society.

It is a great pleasure for one who originated in New Hampshire to return. I sometimes think that those of us who were careless enough to wander away live for the opportunity to get back here. I know that I always get a real thrill whenever I set foot in this state.

Dr. Frank H. Matthews, also a former resident of New Hampshire, and the other delegate from the Rhode Island Medical Society, is ill and could not come. He sends his official greetings to your society and to his many friends in New Hampshire.

I bring to all the members of your society an invitation to attend the summer meeting of the Rhode Island Medical Society, which is to be held at the Viking Hotel, Newport, on May 28 and 29. Any of you who can come will have a cordial welcome.

I shall say one other thing: It seems to be that on this historic occasion for your society, we ought to emphasize one fact, and keep emphasizing it, namely, that there never has been a time in the history of the world when physicians need to stand together more firmly than at the present. We all realize some of the problems of social revolution through which we are going, and the world needs our clear thinking, our careful decisions and our united action; that is why it seems to me most fortunate that in all our gatherings we can have representations from the various states, and that together we can listen to the papers and discussions, and that we can always hold curbstone consultations with each other, so that we may know the thoughts of the various groups and try, in our actions and as we face a troubled and important future, to have the medical profession stand together and think clearly.

Dr. Lucius C. Kingman, Providence, Rhode Island: When our society was founded, your society was just old enough to vote. When it was rumored around Rhode Island that you were to have your one hundred and fiftieth anniversary, there was a little lifting of eyebrows. Then, it was intimated that probably you had to gather in all the Indian medicine men in the community to get enough men to make a society. But, when it was pointed out that Rhode Island did not sign up with the Union until a year after New Hampshire did, they thought possibly there was something in it.

I have still another invitation to bring to you. Dr. Ruggles has already extended the invitation to you to attend our annual meeting at the end of this month at Newport; but I am going to invite you to come to our one hundred and fiftieth anniversary in 1962.

General Bowen then spoke as follows:

I should not wish to have this opportunity pass without appearing before the members of the medical profession in this state to express my appreciation of the wonderful contribution that the physicians have made to the success of the Selective Service System.

As you know, the United States Army is engaged in selecting men on a different basis than was ever done before. These men are not intended to go in for one year's service only, but they are intended to pass into the reserves and remain men who are capable of good field service for ten years. In other words, we are trying to pick men so well that they can remain in storage for that length of time, and that explains why there is so much insistence on the work of the medical profession. It is through the medical service that these men are passing to make this army that we are establishing the best anywhere. In doing that in New Hampshire, we have the services of about one hundred and eighty-five medical officers, all serving without compensation, either as examining physicians or additional examining physicians, members of the medical advisory boards or somewhere else in the service, from the top to the bottom, from the Board of Appeal right down the line.

The amount of work that has been done by these men has been tremendous. Since the registration last October, they have made about 3500 examinations, and these have been detailed examinations, in the course of which they have rejected approximately 45 per cent of the selectees.

That means a lot of work, and destruction, in many cases, of the doctor's regular practice. But, I want to say publicly to all who are here that I have never heard

one complaint from any physician; in fact, some of them have been so interested in this work that they have not even asked for assistance of any kind. In some cases, we have had practically to force a physician to take another man to help him.

In passing, I should also like to mention that we have now arrived at an answer to the great medical problem of the deferment of physicians, of interns and of medical students. This will not be done in a blanket way, but each case will be considered by its local board; and since we will probably know the requirements of the United States Army within the next few months, by next fall you may rest assured that the ranks of the medical profession will not be depleted, nor will the steady flow of young men into the profession, which you need so badly, be interrupted.

On behalf of the National Director, on behalf of His Excellency, the Governor of this state, on behalf of the staff guiding the work of the Selective Service System in this state, and on my own behalf, I thank you all very much. I thank the president of the Society for his continuous co-operation with us in every possible way, and I thank the physicians for the wonderful help that they have given.

I know that we all see that at this time, as in the past, the physicians are ready to make their contributions, both now in preparing an army, and later on the field, if, unfortunately, this great country should be obliged to enter the war.

Captain Wheeler added the following:

General Bowen has asked me to read a few figures concerning the defects that were found, which might be of interest to the medical profession. The figures are correct up to about a month ago.

As General Bowen has said, approximately 45 per cent of those examined were found unqualified for general military service. Some of these were found qualified for limited service, and the others were disqualified.

Of those rejected, about 28 per cent were thrown out because of defective teeth alone. Furthermore, 41 per cent of those rejected had teeth sufficient to reject them, but had other causes, also. But, one might say that, without any other causes, nearly 70 per cent were rejected because of their teeth.

Nine per cent of those rejected were thrown out solely because of eye defects, and about 5 per cent for hernia. Twelve per cent of those rejected had muscular skeletal defects.

A number of men were rejected for so-called "mental causes" — mental deficiency, as well as the psychoses. Over 5 per cent were rejected solely for mental conditions; however, 9.3 per cent of those examined were mentally deficient or mentally defective in one way or another.

The morning session was concluded by an address by Dr. Frank H. Lahey, of Boston, the title being "The Management of Lesions of the Stomach, Duodenum and Jejunum."

The afternoon session convened at two o'clock, with Vice-President Charles H. Dolloff, presiding.

The Secretary, Dr. Carleton R. Metcalf, gave a résumé of the actions of the House of Delegates, and Dr. Deering G. Smith, delegate to the House of Delegates of the American Medical Association and chairman of the Committee on Medical Preparedness of the Society, repeated, in part, his report as given to the House of Delegates of the Society.

The report of the Trustees was then presented by Dr. Henry O. Smith.

FINANCIAL REPORT OF THE TRUSTEES OF THE NEW HAMPSHIRE MEDICAL SOCIETY FOR THE YEAR ENDING MAY 13, 1941

Receipts

Interest on various deposits, other than Benevolence Fund	$420.47

Expenditures

Transferred to Benevolence Fund	$1,000.00
Trustees of Dartmouth College	2,000.00
Pray and Burnham prizes	150.00
Total expenditures	$3,150.00
Decrease in funds, other than Benevolence Fund	$1,729.53

GENERAL FUND

Deposits: New Hampshire Savings Bank	$5,754.05
Portsmouth Trust and Guarantee Company	3,470.76
Nashua Trust Company	1,672.50
Total funds available May 13, 1941	$10,897.31

BARTLETT FUND

Deposit: Portsmouth Savings Bank ($352.11 of this is a permanent fund, the income to be "expended only for the benefit of medical science, as may be directed by vote of this society")	$4,643.26

PRAY FUND

Deposit: Strafford Savings Bank ($1000 of this is a permanent fund, the income to be expended only for prize essays)	$1,294.00

BURNHAM FUND

Deposit: New Hampshire Savings Bank ($1140 of this is a permanent fund, the income to be expended only for prize essays)	$2,191.00

BENEVOLENCE FUND

Deposit: New Hampshire Savings Bank ($349.81 of this is accrued income available for the purposes of the fund)	$4,224.50

A prize of $100 was awarded for a paper entitled "Scientific Medicine in General Practice" by "Edward E. Hale," pseudonym for Dr. Oliver S. Hayward, of New London, New Hampshire. It is expected that prizes will be offered in 1941–1942, and notice will be sent to the members of the Society in due time.

The accounts of the Treasurer of this Society have been examined and found correctly cast and properly vouched.

HENRY O. SMITH
SAMUEL T. LADD
FREDERIC P. LORD

Dr. Stanley B. Weld, of Hartford, Connecticut, then spoke concerning the National Physicians' Committee, and was followed by Dr. Jones, who delivered the presidential address, entitled "Orthopedics in New Hampshire." The scientific session was concluded by a talk, "The Work of the Medical Examiner," by Dr. William J. Brickley, of Boston.

The banquet was held at the Hotel Carpenter at six-thirty o'clock, with Dr. David W. Parker, of Manchester, as toastmaster. Following the opening remarks of Dr. Parker, President-Elect Charles H. Dolloff, of Concord, and President Jones spoke briefly. Dr. Harry H. Amsden, of Concord, then gave an address, "The Doctor of One Hundred and Fifty Years Ago." Dr. Frederic P. Lord, of Hanover, spoke concerning the prominence of the Mussey family in the medical history of New Hampshire, and introduced William C. Mussey; he then gave a short account of the equally prominent Smith family, and introduced Dr. Henry O. Smith, Dr. Deering G. Smith and Robert G. Smith. Dr. Henry O. Smith, of Hudson, described the career of Dr. Josiah Bartlett, the founder and first president of the Society, and introduced Mrs. Levi S. Bartlett and Mrs. Lottie Goodrich, the latter a direct descendant of the founder. Dr. Marion Fairfield, of Nashua, then read the appreciation of Dr. Bartlett pronounced by Dr. Thomas W. Luce, at the time of his retirement as president of the Society.

In passing out of the picture as the retiring president, I want to use the time at my disposal in talking to you about the man who first held the office I am being relieved of today. It has long been the custom of most presidents of this society to refer to their predecessors in the office in some complimentary way. This seems to me a fitting thing to do, because some very able men, and, indeed, some very eminent men, have been presidents of this society. To my mind, however, no one in this long list of incumbents, covering the whole period of one hundred and thirty-five years, has ever quite measured up to our first president, Josiah Bartlett.

His history is probably well known to most of you, and its recapitulation at this time may seem trite. I have, however, been led to select him as my theme tonight for two reasons. First, this happens to be the sesquicentennial of the Declaration of Independence, which he did so much to bring about, and next because I believe his story should be told here once in a decade or so by someone, lest we forget our great inheritance.

Josiah Bartlett, then, was born in Amesbury in 1729. At the age of sixteen, he went into the office of a relative, Dr. Ordway, and began the study of medicine. This was some twenty years before our first medical school was established in Philadelphia, and physicians were made in those days just as carpenters and blacksmiths were made, by a five to seven years' apprenticeship with a master.

Josiah had been well grounded in the three R's; he had a good elementary knowledge of Latin and Greek; and he was a good student. He had the clinical advantages afforded by Dr. Ordway's large practice and also the use of his very good library. He did a great deal of dissecting during the five years of his term with Dr. Ordway, and he became a very proficient anatomist; also his notes on his study of plant life give evidence of good knowledge in this field.

In 1750, when he was twenty-one years old, he settled in the town of Kingston and commenced a medical practice which he continued for forty-five years. He was a close and careful observer and quite early in his medical career he discovered what he believed to be gross errors in the then accepted pathology and treatment of several diseases, and with a boldness which always followed his convictions, he inaugurated many medical reforms, some of which almost constitute marking stones of medical progress in New England. His crowning medical achievement from our viewpoint, perhaps, was the founding of this society. He secured its charter, wrote its constitution and by-laws, and then, associating with himself eighteen other physicians of the state, all men of prominence in their profession, he formally organized this society on February 16, 1791. He was naturally made the first president, and was re-elected for four successive terms.

Quite early in life, he became interested in military affairs and gradually rose to be a colonel in the King's militia, and was at that time the highest ranking military officer in the state. His colonel's commission was recalled, and his house in Kingston was burned by a spy in 1774, because of his patriotic activities, but many of our New Hampshire soldiers who distinguished themselves under General Stark at Bunker Hill and Bennington, and at Burgoyne's surrender, and later under General Washington in the southern campaigns, received their military training from Colonel Bartlett.

While with Dr. Ordway and during the early years of his professional life, he whiled away his spare time in reading law books. He somehow acquired a knowledge of the law, which, combined with his sound sense and judgment, was recognized in 1780 in his appointment as a justice in the Court of Common Pleas. In 1787, he was elevated to the Supreme Court of New Hampshire. When we recall the national reputations of some of the New Hampshire lawyers of his period, we have to believe that his standing as a justice must have been far from mediocre.

Josiah Bartlett frequently represented his town in the legislative assembly, and in 1775, he was elected to the Continental Congress. When the greatest state paper ever conceived by the mind of man came up for a vote of ratification, the roll was called by states — New Hampshire, the northernmost state, was called first and Georgia, the southernmost, last. Thus, Josiah Bartlett was the first member to vote yes for the Declaration of Independence, and after that document had been signed by the president of the Congress, John Hancock, the second to sign was Josiah Bartlett. This act has made him immortal, and yet it fell to his lot a few years later to render his country perhaps an even greater service. When the Constitution was submitted to the states, it encountered considerable opposition. It was necessary, if it survived, that nine states accept it. Eight had accepted it when our constitutional convention met in February, 1788, and, as New Hampshire was the ninth state, the attention of the entire nation was directed to this assembly.

Josiah Bartlett, always a resourceful politician, was a member of that convention, and he ascertained quite early that the measure was bound to fail because so many of the delegates, particularly from the smaller towns, were under instruction to vote against it. He, therefore, secured an adjournment until the following June. He then began a very intensive personal campaign for the constitution and was rewarded, when the convention reconvened, by a 57 to 46 vote for its acceptance. So we may possibly owe to the energy and wisdom of Josiah Bartlett some of the greatly vaunted constitutional rights and privileges that we enjoy today.

New Hampshire was the first state to have a constitution of its own, and that constitution, under which we live and do business today, was very largely written by Josiah Bartlett. He was the first governor of the state under that constitution, and was re-elected for four successive terms. He was then elected a member of the United States Senate, but was unable to serve because of physical infirmities.

He brought up a family of twelve children. Three of his sons and seven of his grandsons became doctors of medicine.

All this I submit as a brief survey of some of the outstanding events in the career of a remarkable man.

Josiah Bartlett is described by his contemporaries as a tall man of fine figure, affable but dignified in his manner and very particular in his dress. He wore his auburn hair in a queue, a white stock at his throat, ruffles at his wrists, short clothes, silk hose, low shoes with silver buckles. One writer, the Rev. Dr. Rollins, describes his bearing as that of "an Athenian philosopher, fine and aesthetic, curiously mingled with Yankee shrewdness, cool and practical."

In Amesbury, the house in which he was born is owned and maintained by the Josiah Bartlett Chapter of the Daughters of the American Revolution. His bronze statue standing in the square was unveiled in 1888, and Whittier's poem, "The Signer," was written for the event. His picture hangs on the wall in our state house, and the town at the southern entrance to our beautiful Crawford Notch is named in his honor.

In the town of Kingston, on a slight elevation overlooking the village green, still stands the fine, old-fashioned house that he built and lived in, after his first house was burned in 1774. It has always been owned and occupied by his descendants. It is in a good state of preservation and is literally filled with Josiah Bartlett's belongings. Its present mistress, Mrs. Levi S. Bartlett, is always glad to welcome anyone who may be interested and takes delight in showing the house and the doctor's things.

It seems to me that we, as members of this venerable society which he founded, as well as sons of the State and Nation which he helped to found, may well regard this fine old mansion as our particular shrine, to which we should feel in duty bound to make at least one pilgrimage, in humbleness of heart, and, as has been said by a former president, hope to gain from such an experience at least some degree of that rare devotion to our profession and to our country that characterized Josiah Bartlett.

Across the green from the house is the old tavern and in the rear of this is the village cemetery, in one corner of which a plain pile of cut granite marks the last resting place of the first president of this society. The inscription states that he died May 19, 1795, in the sixty-fifth year of his life.

And now, in closing, I want to read to you the last words of his message to this society as its retiring president. This was written and sent out from his sickroom in that old house in Kingston and was read at the annual meeting held in Concord in 1794. These words are, and perhaps were intended to be, as much a message for us of today, as they were for those members who listened to them as they were read, in this very place, one hundred and thirty-two years ago:

> That the members of this Society may be useful to themselves and the public, and enjoy that exalted pleasure that arises from a consciousness that they have contributed to the health and happiness, not only of their patients, but, by communicating to others the knowledge and cure of disease, to the general happiness of the human race, is the ardent wish, Gentlemen, of your very humble servant, Josiah Bartlett.

Governor Robert O. Blood spoke concerning the increasing participation by the State in matters pertaining to medical care, and the program was concluded by Dr. Lahey, who recounted many of the current problems facing the medical profession in the United States.

MEDICAL PROGRESS

TREATMENT OF MENINGITIS*

MAXWELL FINLAND, M.D.,† AND JOHN H. DINGLE, M.D.‡

BOSTON

PRIOR to 1936, recoveries from acute bacterial meningitis due to organisms other than the meningococcus were quite rare, in spite of laborious and often heroic therapy of many sorts. The mortality in the meningococcal cases was likewise very high, in spite of the almost universal use of specific serums and other measures. The results reported[1-3] in several large series of cases are probably typical, although small groups of cases with more favorable results from various therapeutic procedures were occasionally reported.

Tripoli[1] summarized the results of different kinds of treatment at the Charity Hospital in New Orleans between 1925 and 1934. His series included 221 cases of meningococcal meningitis with a mortality of 65 per cent and 247 other cases of nontuberculous acute meningitis with only 3 recoveries. All the patients with meningococcal meningitis received antiserum intravenously and intramuscularly, but the lowest fatality rates (42 and 48 per cent) were obtained in those patients who received intraspinal and intracisternal injections in addition.

Lindsay, Rice and Selinger[2] reviewed 331 cases of meningitis treated at the Children's Hospital in Washington during the ten-year period from 1924 to 1933. The mortality was 40 per cent in 58 cases of meningococcal infection, whereas only 3 patients recovered among 133 with other proved bacterial etiology after the tuberculous and the syphilitic cases were excluded.

Neal[3] summarized 3178 cases occurring in New York City during a twenty-five-year period prior to 1935. In this series, there were 829 cases due to bacterial agents other than the meningococcus or the tubercle bacillus, with only 24 recoveries. In an earlier paper, Neal and her associates[4] had reported 302 cases of meningococcal meningitis for whose treatment they were responsible. These cases occurred during a five-year period prior to 1931, and the mortality in this series was 18.3 per cent. Walsh,[5] however, estimated that the mortality from cerebrospinal fever in the United States from 1920 to 1936 averaged over 50 per cent.

As with most other serious acute bacterial infections, chemotherapy with the sulfonamide drugs has almost completely revolutionized the management and the prognosis in cases of acute purulent meningitis. The successes from chemotherapy alone have been so frequent and so striking by contrast with previous results that many of the specific therapeutic measures and other procedures formerly thought to be helpful and even essential are rapidly being discarded. In this report, we shall summarize the current opinions concerning the chemotherapy and specific serotherapy of acute meningitis due to some of the commoner bacterial agents, and shall consider the present status of some of the nonspecific therapeutic procedures previously employed. A more comprehensive review of the recent literature, particularly that dealing with meningococcal meningitis, has been prepared for publication elsewhere.[6] Keefer's[7] recent clinic also contains a summary of important features concerning the pathogenesis, diagnosis, prognosis and treatment of meningitis.

GENERAL ASPECTS OF TREATMENT

Meningococcal Meningitis

Cerebrospinal fever has long been recognized as a "scourge of armies." This is due to the spectacular nature of the clinical manifestations and not to a high attack rate or to a high fatality rate. The disease usually strikes in an almost mysterious way, without warning, thus having a marked depressing effect on the morale of the military personnel.[8] During World War I, there were 5839 cases of meningococcal meningitis in the United States Army, with 2279 deaths.[9] The disease was also quite prevalent in this country during the late twenties, spreading from the West Coast through the Middle West, but tending to spare the cities of the Atlantic Seaboard.[8] In recent months, there have been a considerable number of

All articles in this series will be published in book form: the current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. $4.00).

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine and the Department of Bacteriology and Immunology, Harvard Medical School.

This study was aided in part by a grant from the William W. Wellington Memorial Research Fund, Harvard Medical School.

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cases in Nova Scotia,[10] and in Great Britain some 12,500 cases were reported during 1940.[11] Further outbreaks are likely to occur in this country in the near future.

Chemotherapy. Soon after the recognition of the effectiveness of sulfanilamide against the hemolytic streptococcus, Buttle, Gray and Stephenson[12] reported that this drug was also effective against meningococcal infections in mice. Since that time, sulfanilamide and several of its derivatives have been used widely and effectively in the treatment of cerebrospinal fever in human beings. Reliable figures of case fatality rates with chemotherapy alone are difficult to obtain, however, for several reasons: there were wide variations in mortality rates, both with and without serum, before the introduction of chemotherapy; from many of the reports, it is not possible to determine the number of cases receiving any one kind of therapy, and many patients received more than one kind of treatment; some of the fatal cases have often been excluded for a variety of reasons; data concerning the factors that influence the outcome have not always been presented in adequate detail. Nevertheless, it is abundantly evident that chemotherapy alone is highly effective in curing this disease, even under the most unfavorable conditions.[13, 14]

From a tabulation of some of the recent reports, the mortalities in sulfonamide-treated cases of meningococcal meningitis, based on groups of from 200 to over 1000 cases, are estimated as follows: with sulfanilamide alone, 14 per cent; with sulfanilamide and antiserum, 25 per cent; with sulfapyridine alone, 8 per cent; and with sulfapyridine in addition to antiserum, 12 per cent. Only small numbers of cases treated with sulfathiazole have been reported to date,[15–17] but the results in these cases seem to compare favorably with those obtained with sulfapyridine. In view of the low concentrations of sulfathiazole that are obtained in the cerebrospinal fluid during treatment,[18, 19] it would seem either that this drug is highly effective in low concentrations or that the level of the drug in the cerebrospinal fluid is not by itself of particular consequence. At any rate, so far as meningococcal meningitis is concerned, the warnings against the use of sulfathiazole based on this factor do not now seem to be justified. Sulfadiazine has also proved to be as effective as any of the other drugs in the few cases in which it has been used.[10] Since, when properly used, sulfadiazine appears to be less toxic than the other accepted sulfonamides, it may prove to be the drug of choice in the treatment of meningococcal infections.

Serotherapy. The difficulties in evaluating the results of serotherapy alone in cerebrospinal fever have been pointed out in a previous progress report.[20] To determine with scientific precision whether, in actual practice, antiserum is of value as a supplement to sulfonamide therapy is almost impossible. This is obvious from a study of the data on which the mortality figures mentioned above are based, and also from a consideration of the difficulties involved in the use of serums. Combined therapy is usually reserved for the severest cases, or else antiserum is given as a supplement to the sulfonamides in individual cases only after it begins to appear that the sulfonamides alone have failed to effect the desired cure.

Banks[21] has been sufficiently impressed with the results that he has obtained with chemotherapy alone to take the view that serum therapy is now unnecessary even as an adjuvant to chemotherapy. Other results from Britain suggest, however, that the mortality under chemotherapy is still over 20 per cent.[22, 23] The accuracy of these figures is, of course, open to question. Experimentally, the combination of sulfonamide and antiserum is more effective in curing meningococcal infections in animals than either agent alone.[24] Until more convincing data become available, therefore, it seems appropriate to reserve the immediate use of antiserum as a supplement to chemotherapy for the very severe or the apparently fulminating cases. It is particularly recommended for patients in coma in whom bacteremia is suspected. In other cases, antiserum need be employed only when there is no definite objective evidence of marked improvement after twenty-four to forty-eight hours of adequate chemotherapy. In any event, the serum used should contain antibodies specific for the infecting strain, and should be given intravenously in large doses with the usual precautions. Intrathecal administration should probably be avoided, at least until one is convinced that the disease is not being controlled adequately with drugs and intravenous antiserum.

The relative merits of antitoxin and antibacterial serum are still undecided. Hoyne[25, 26] advocates the use of antitoxin, although experimentally it appears to show no properties other than those due to the antibacterial immune bodies that it contains.[27–29]

Certain details concerning therapeutic procedures and diagnostic methods will be considered later.

Streptococcal Meningitis

The mortality in cases of streptococcal meningitis has been reduced from over 95 per cent to less than 35 per cent by the use of sulfonamide

drugs.[30–33] Sulfanilamide was the first drug to be used in this disease and, since it has proved highly effective, is still preferred by most physicians. Sulfapyridine is probably more effective, and successes with it have been reported. The use of other sulfonamides has not been reported in sufficient numbers of cases to warrant any opinions. Sulfathiazole should probably not be used because it is less effective against the streptococcus, in addition to the fact that high levels of this drug are difficult to maintain even in the blood. Sulfadiazine has proved to be highly effective in some other streptococcal infections[34] and will probably become the drug of choice, but data concerning its use in meningitis are not yet available.

Recoveries under sulfonamide therapy have been reported not only in meningitis caused by beta-hemolytic streptococci, but also in cases due to *Streptococcus viridans*[35–37] and even in isolated cases due to anaerobic streptococci.[38]

Antistreptococcus serums are probably of little or no value. Scarlet-fever antitoxins or convalescent serums, however, have been employed in some cases of postscarlatinal or other streptococcal meningitides. Apparently beneficial results have been reported from their use either alone or as a supplement to chemotherapy.[3, 39, 40] They are probably best reserved for patients with severe toxemia, especially when a rash is present.

Pneumococcal Meningitis

There can be little doubt that almost all the numerous cases of recovery from pneumococcal meningitis that have appeared in the literature during the past four years are attributable directly to the use of sulfonamide drugs, since only isolated patients were previously known to survive this disease. Several authors,[41–46] in reviewing the recent literature, have estimated the mortality in sulfonamide-treated cases to be about 35 per cent. This seems to us to be a deceptively low figure, since the great majority of failures remain unreported. Our recent experience suggests that the gross mortality in unselected cases receiving sulfonamide therapy, with or without other measures, is more nearly 80 per cent. Recoveries, however, have been reported in very severe and bacteremic cases,[47] in infants,[48–50] and even when the disease is complicated by cavernous-sinus thrombosis.[51]

Specific antipneumococcus serums, alone or supplemented by various forms of drainage, may have been responsible for some recoveries prior to the introduction of sulfonamide therapy.[42, 52–54] In experimental Type 1 pneumococcus meningitis in rats, a greater percentage of recoveries may be obtained from the combination of specific antiserum and sulfanilamide than from either agent used separately.[55] This is difficult to demonstrate in human cases, although many of the recent reports of recoveries suggest that antiserum may have played a significant role when used to supplement chemotherapy.[42, 45, 48, 56–59] The antiserums were given intravenously in all cases, but intrathecal injections, with or without complement, were used in some.

Sulfanilamide, which is known to have only relatively slight bacteriostatic action against the pneumococcus, has apparently been solely responsible for a number of the reported recoveries.[46, 60] It is our belief that in such cases the immunologic conditions were favorable, or that the organisms were highly susceptible or that both these factors were operative. Finland and his co-workers,[59] just before the introduction of sulfapyridine, reviewed the immunologic aspects of pneumococcal meningitis and outlined a therapeutic regime based on what was then known of the action of sulfanilamide and on the supposed mechanism of recovery in sulfanilamide-treated cases. This regime included intensive treatment with sulfanilamide supplemented by intravenous antiserum and the intrathecal injection of antibodies and complement. It was realized that the administration of antibody probably was not essential in all cases and that, in practice, the intrathecal treatments would be necessary only in selected cases. It was to be expected, of course, that the introduction of more powerful antipneumococcus sulfonamides would reduce the necessity for serum therapy in many cases. Indeed, recent experience has indicated that a high percentage of recoveries may be expected from chemotherapy alone if intensive treatment with such drugs is undertaken from the beginning. Thus, the intravenous use of sodium sulfapyridine to initiate treatment and to maintain high blood concentrations during the first one or two days of therapy was probably responsible for the large proportion of recoveries in some of the recent reports.[47, 61]

Data on the uses of sulfathiazole and sulfadiazine in pneumococcal meningitis are scant, and judgment concerning the value of these drugs must therefore be reserved. Sulfadiazine seems to be advantageous, since it is effective in other pneumococcal infections and higher levels can be maintained with relatively fewer toxic effects when it is properly used.

Ross[62] reported a case of pneumococcal meningitis in which "drug resistance" was apparently acquired in the course of two or three days

of treatment with sulfapyridine. This occurrence is probably quite rare. Schmidt and Sesler[63] have recently shown that pneumococci that have become resistant to sulfapyridine are just as susceptible to hydroxyethylapocupreine as the parent strains. Since it has been shown that pneumococci which have become resistant to one effective sulfonamide are equally resistant to others,[64, 65] it may be necessary to resort to hydroxyethylapocupreine in cases in which sulfonamide fastness can be proved.

Influenza-Bacillus Meningitis

The gross mortality in untreated cases of this disease is over 90 per cent, and the most vital single prognostic factor is the age of the patient. Almost all infants less than two years of age succumb.[66] Of the six known types of *Haemophilus influenzae*, Type *B* produces the great majority of the meningeal infections in infants and children. Most of those in older patients are probably due to other types or to the rough strains normally found in the respiratory tract. It seems likely that many of the spontaneous recoveries and the recent successes with chemotherapy alone occurred in patients infected with these rough or respiratory strains. There is, of course, no relation between influenza-bacillus meningitis and epidemic influenza, the latter now being known to be due to a specific virus.

Although there are a number of reports of recoveries from sulfonamide drugs alone, most of these occurred in the older age groups. The sum total of the results, although encouraging, is not very striking.[56] Many observers failed to obtain any favorable results with the use of drugs only, and that has been our experience. Final judgment on the effectiveness of sulfonamides alone, however, awaits more extensive data.

During the past few years, specific antiserum prepared in horses has been used intravenously and intrathecally, both with and without complement, in the treatment of meningitis due to the Type *B* influenza bacillus. Although the gross mortality may have been reduced to about 80 per cent,[67] the results in general have been far from satisfactory. More recently, however, rabbit antiserum specific for Type *B* has been used with encouraging results.[56, 68] Most of the patients treated with rabbit antiserum received chemotherapy in addition, and the role of each of these agents is thus difficult to evaluate. Davies[69] has treated a few patients with rabbit antiserum alone, and his results seem to indicate that this single agent may be as effective as the combined therapy.

The treatment recently outlined by Alexander[56] is as follows: sulfanilamide should be administered immediately; fluids should be forced for three hours; and the equivalent of 25 mg. of antibody nitrogen intrathecally and 50 to 75 mg. of antibody nitrogen in a slow intravenous drip diluted in physiologic saline, Ringer's or sulfanilamide solution, should be given. The object is to neutralize all the free antigen and to establish and maintain an excess of antibody in the blood and cerebrospinal fluid. Such an excess is present when the serum gives rise to capsular swelling with the homologous organisms, or when the skin reaction to the specific polysaccharide is positive.[70] It is not certain whether the intrathecal treatment is essential. Information concerning the relative merits of the various sulfonamides is also lacking.

Staphylococcal and Other Bacterial Meningitides

Recoveries from staphylococcal meningitis have been reported from the use of sulfanilamide,[71, 72] but successes have been more frequent with the use of sulfathiazole.[73–77] There have been 2 recoveries with sulfathiazole treatment at the Boston City Hospital. Sulfadiazine may also be useful in this condition, since it is highly effective against the staphylococcus.[34] Lyons[78] reported 2 cases of bacteremic cavernous-sinus thrombophlebitis treated successfully with a combination of sulfathiazole and heparin. One of these patients had clinical signs of meningitis that were confirmed by lumbar puncture.

Isolated cases of meningitis due to a large variety of other bacteria have been treated successfully with various sulfonamide drugs. These have included, among others, infections with colon bacilli,[79] Salmonella organisms,[80] Friedländer's bacillus,[81] gonococcus[82] and *Micrococcus tetragenus*.[83–85] Various sulfonamides have been used in these cases, either singly or in succession.

Diagnosis

The final etiologic diagnosis in any case of meningitis must be made on the basis of isolation or immunologic identification of the organism. The recent use of certain laboratory technics, mentioned below, permits an immediate final diagnosis in some cases. With the pneumococcus, for example, final diagnosis of both the organism and its type may be made merely from a stained smear and from capsular swelling with rabbit typing serum.

Clinical differentiation of the various etiologic types of meningitis is usually not possible. Certain general statements, however, may be made. During an epidemic of cerebrospinal fever, if evidences of purulent meningitis are present, the most probable etiologic agent is the meningococ-

cus, and the patient should be so treated, even though organisms are not found. Meningitis associated with otitis or mastoiditis is most probably due either to the pneumococcus or to the streptococcus. When an upper respiratory infection precedes meningeal involvement, the likeliest organisms are the pneumococcus, the streptococcus and, in children, the influenza bacillus. If furuncles are present on the face or elsewhere, staphylococcal infection is probable. It should be remembered that in infants and young children the influenza bacillus is being recognized as one of the most frequent causes of meningitis.

Although primary meningitis is usually due to a single organism, mixed infections may occur. These may be either simultaneous or consecutive infections. Such mixed infections are rare and, when they occur, usually follow primary infections outside the central nervous system.

The etiologic diagnosis is made in the usual way by cultures of the cerebrospinal fluid, the blood and pus from focal infections. Several recent technics have facilitated an early diagnosis. The capsular swelling reaction may be carried out directly on the spinal fluid, on its sediment or on the initial culture after the morphology and staining characteristics have been determined by the methylene blue and Gram's stains. This method is of particular value with the pneumococcus, influenza bacillus[86] and Type 1 meningococcus.[87] The technic is similar in all respects to that employed in typing pneumococci in sputum. The precipitin test, employing specific antiserum and the clear supernatant spinal fluid, may be of value. This procedure may be used not only for etiologic identification of the causative organism, but also for typing the pneumococcus and the influenza bacillus. The test has also been employed in meningococcal infections, but in these direct typing may be complicated by the presence of the group-specific C substance.[88] In some patients, the infecting organism may be obtained from cultures of the nasopharynx early in the disease. The meningococcus is almost always found there in cases of cerebrospinal fever.[89] Mueller and Hinton[90] have recently described a simplified medium for the cultivation of the meningococcus. This medium has proved satisfactory for the primary isolation of gonococci and meningococci.[10] The growth of meningococci is facilitated by increased tension of carbon dioxide, which may be accomplished simply by the use of a candle jar.[91]

Focal Infections

The elimination of focal infections is of the utmost importance because of the tendency of meningeal infections to become refractory to therapy if such foci are not removed. If the focus is apparent and if the local reaction is sufficiently advanced, immediate operation should be carried out for the relief of pressure and evacuation of pus. Often, however, it is difficult to localize the focus. In a recent article, Keefer[7] has indicated a number of signs that aid in the differential diagnosis. In general, chemotherapy should be instituted for twelve to twenty-four hours before operative procedures are undertaken, and should be continued for several days thereafter. The extent of the operation should be sufficient to eliminate nonvital tissue, particularly necrotic bone. Cultures should be made from all purulent foci at the time of operation.

Lumbar Puncture

The present tendency among some clinicians who are treating patients with meningitis is to avoid doing lumbar punctures, even to the extent of eliminating the procedure completely. This is an extreme view that is probably not justified. First of all, an initial lumbar puncture is necessary to establish the diagnosis of meningitis and to determine the etiologic agent. This is still extremely valuable to ensure the choice of the most effective drug and of the specific serum. With the usual precautions, the procedure does not jeopardize life or interfere with the subsequent recovery of the patient. In a recent review, Pray[92] found that lumbar puncture is not a significant factor in inducing meningitis, even in bacteremic patients. His data suggest that there may be a greater risk to the patient through failure to recognize the presence of meningitis if this procedure is not carried out. The first spinal fluid should be collected aseptically in separate tubes for culture and for chemical determinations. Estimation of the glucose content is the most valuable of the chemical determinations, since a low level is consistently found in bacterial infections. Total and differential cell counts should also be carried out, since they are of aid in distinguishing bacterial infections from those due to other agents. Thus, in tuberculosis, syphilis and the virus diseases (lymphocytic choriomeningitis, equine encephalomyelitis, St. Louis encephalitis and so forth), mononuclear cells predominate. In the course of differential counts, typical organisms are sometimes recognized in torula infections.

Lumbar puncture should be repeated for specific indications: for relief of the signs and symptoms of increased cranial pressure; to determine the progress of the case; to establish cure; for the diagnosis of relapse or recurrence; and for intra-

thecal therapy with antiserum when other methods of therapy fail.

Choice of Sulfonamide Drugs

It should be clear from what has already been said that all patients with acute bacterial meningitis should receive sulfonamide therapy, but no hard and fast rule can be set down regarding the choice of drugs or the indications for specific serums and for other measures. The number of adequately studied cases is too small to warrant definite opinions. This is particularly true of the use of sulfadiazine in all kinds of meningitis and of all the drugs in infections due to influenza bacillus and the less common organisms. With these reservations, the following is our own tentative order of preference of sulfonamide drugs for various kinds of acute bacterial meningitis:

Causative Organisms	Order of Choice			
	Sulfadiazine	Sulfathiazole	Sulfapyridine	Sulfanilamide
Meningococcus	1	3	2	4
Streptococcus	1	4	2	3
Pneumococcus	1	3	2	4
Influenza bacillus	?	?	?	?
Staphylococcus	1	2	3	4
Gram-negative bacilli	1	2	3	4
Other pyogenic organisms	1	2	3	4

Indications for the Use of Specific Antiserums

Regarding the use of specific antiserums as a supplement to chemotherapy, there is considerable disagreement among competent authorities. In our opinion, much depends on the particular conditions presented in each case. The following factors must be considered: the availability of potent specific antiserum against the infecting strain; the severity of the disease — severe cases may proceed so rapidly to a fatal outcome that one cannot afford to temporize, and it is probably better to be wasteful of serum than to regret having missed the opportunity to use it; the response of the patient to adequate doses of sulfonamides; when foci of infection prevent an adequate response to drugs, specific serums are useful, not in preference to removal of these foci but as an additional measure.

With these factors in mind, we now believe that the following recommendations are justifiable. Antimeningococcus serums should be given to patients with Type 1 infections as soon as the etiologic diagnosis is made only when the disease appears to be severe or fulminating. In other cases, such serums may be used if the infection fails to respond to adequate chemotherapy within twenty-four to forty-eight hours. A favorable response is indicated by the disappearance of fever, the failure to recover organisms from the cerebrospinal fluid and the return of the level of sugar in the cerebrospinal fluid to normal. In meningitis due to pneumococci of known types, homologous specific rabbit antiserums should be used under the same conditions. *All* patients with Type *B* influenza bacillus meningitis should receive specific rabbit antiserum as soon as the organism is identified. Scarlet-fever antitoxins or convalescent serums may be used in severe and toxic streptococcal meningitis, particularly if it is associated with a rash or if it occurs in the course of scarlet fever or as a complication of that disease.

Dosage and Route of Administration of Drugs and Antiserums

The recent trend in the dosage of sulfonamide drugs is to give large amounts during the early stage of treatment, to try to maintain as high a level as is consistent with safety and comfort until the infection is well under control, to give fairly large amounts of fluids (3000 to 4000 cc. a day) and to continue drug treatment in the same or in slightly reduced doses for fairly long periods, to ensure against relapses.

The intravenous use of 0.8 per cent sulfanilamide in physiologic saline solution or of a 5 per cent solution of the sodium salts of the other common sulfonamides in distilled water is usually recommended. It is used for the initial dose and for the first twenty-four to forty-eight hours of treatment in all patients and also later in those who vomit excessively or fail to maintain adequate blood levels. We have preferred to use the sodium salts of the sulfanilamide derivatives dissolved in physiologic saline solution — 1 to 2 per cent for intravenous use (larger concentrations precipitate out at room temperature) and 0.5 to 0.7 per cent for subcutaneous injections. The latter route is preferred for all but the initial injection when parenteral therapy is desired, and, in our experience, this produces no local reactions. The daily dosage is 6 to 9 gm., depending on the weight, for each of the drugs. This total amount is given as the initial intravenous injection, and a similar amount is given daily in three equal portions at eight-hour intervals for sulfanilamide, sulfapyridine and sulfathiazole, and in two equal parts every twelve hours when sulfadiazine is used. Oral administration is used as soon as the condition of the patient permits, and the daily dose is then given in six equal parts at four-hour intervals. Treatment is usually continued after complete clinical and bacteriologic evidence of recovery for two to five days in meningococcal infections, for ten to fourteen days in pneumococcal and streptococcal cases, and for two to three weeks in all other cases.

Intrathecal injections of sulfanilamide or of sodium sulfapyridine are still recommended by some authorities, but most of them caution against the use of sulfonamides by this route. There is some evidence from the recent results in sulfathiazole-treated cases to suggest that the concentration of drug in the spinal fluid may not be of significance per se, although this point is not yet proved.

When specific serums are used, they should be given intravenously (or intramuscularly, if necessary). The amount should be such as to establish and maintain an excess of antibody in the circulating blood. This may be demonstrated in infections due to pneumococci and influenza bacilli by capsular swelling of the patient's organism in his serum or by the immediate positive skin test with the homologous type-specific polysaccharide.[70]

Intrathecal injections of serum are probably not necessary in most cases, and some experienced physicians now advise against their use under any circumstances. We believe that the intrathecal use of antiserum should be reserved for patients who fail to respond favorably to adequate chemotherapy and intravenous serotherapy, thirty-six to forty-eight hours being allowed to elapse after adequate intravenous therapy. The advisability of the additional use of complement (fresh human serum) with intrathecal antiserum seems to be very debatable at present. In pneumococcal meningitis in adults, both antibody and complement may be given intrathecally in the least irritating form by using fresh serum obtained from the patient after a sufficient excess of antibody has been established by intravenous therapy.[59]

Complications

Complications of meningitis have been remarkably rare in patients who have recovered following sulfonamide therapy. Deafness is still the most frequent complication in the cases of cerebrospinal fever and has also been observed in patients recovering from pneumococcal meningitis. Hydrocephalus is also seen in infants recovering from all kinds of meningitis. Relapses are not infrequent. The diagnosis and treatment of the relapse are essentially the same as those of the original infection.

Prophylaxis

For the prevention of epidemics of cerebrospinal fever in military forces, Mink[93] and Zinsser[94] have proposed gradual mobilization and "hardening" of new recruits. Laybourn[95, 96] advocates the search for and isolation of chronic meningococcal carriers. Treatment of carriers with antiseptic sprays[89, 97] has been attempted, but the results are not conclusive. Sulfonamide drugs have been tried recently with some encouraging results.[98, 99] Penicillin as a snuff[100] and tyrothrycin as a spray[101] are now receiving a trial for the eradication of carriers.

The prevention of pneumococcal and streptococcal meningitis depends on the care of foci of infection and of injuries in and about the head. The use of sulfonamide drugs is recommended in the treatment of otitis and mastoiditis and also during and after all operations in which the cranial cavity is or may be entered.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27471

PRESENTATION OF CASE

A thirty-year-old man was admitted because of increasing difficulty in breathing.

The patient had been well until a month before entry, when there was sudden onset of cough, productive of purulent sputum. Nine days later, night sweats and chills appeared. When admitted to a sanatorium three days later, the patient was acutely ill and dyspneic, with rapid pulse and high fever. There was dullness throughout both lung fields, with a few medium rales in the left. On the fifteenth day of the illness, the blood showed a red-cell count of 4,950,000 with 85 per cent hemoglobin, and a white-cell count of 4400 with 79 per cent polymorphonuclears, 9 per cent lymphocytes, 11 per cent monocytes and 1 per cent basophils. A week later the white-cell count was 4500, and three days after that it rose to 6400 with 91 per cent polymorphonuclears. The sedimentation rate was 8 mm. The tuberculin test was negative up to 1 mg. The urine was essentially normal. Culture of the sputum showed mixed organisms, with staphylococci predominating; on another examination, a pure growth of hemolytic staphylococcus was isolated. Tubercle bacilli could not be found by concentration tests. Agglutination tests for typhoid and paratyphoid fevers, undulant fever and tularemia were negative. A course of sulfathiazole was given from the twentieth to the twenty-seventh day of the illness, and a blood level of 4 mg. per 100 cc. was attained. The drug was discontinued because of the appearance of a rash, and because of the absence of benefit. The patient continued acutely ill and febrile. His pulse ranged from 120 to 138, with respirations from 46 to 48. There was increasing cyanosis and dyspnea.

The past and family histories were not of significance.

On admission, the patient appeared thin and wasted. The skin and mucous membranes were quite cyanotic. The lips were covered with sordes, and the nostrils bore crusted hemorrhagic lesions. The trachea and heart were displaced to the left. Loud wet rales were heard over each upper-lung field, with loud tubular breath sounds, and resonance was preserved in these areas. There were small moist rales in the lower two thirds of the right chest, with absence of breath sounds and with percussion dullness. A pleural friction rub was heard at the left base. The heart sounds were obscured by the lung noises. The abdomen was slightly tympanitic. Rectal examination was negative. There was well-defined pitting edema of both legs. The calves were soft, cool and free from tenderness.

The temperature was 102°F., the pulse 138, and the respirations 50. The blood pressure was 120 systolic, 75 diastolic.

Examination of the blood showed a white-cell count of 15,000 with 80 per cent polymorphonuclears. The red-cell count was essentially as noted in the other hospital. The nonprotein nitrogen of the blood was 23 mg. and the total protein 4.5 mg. per 100 cc.; the chlorides were 88 milliequiv. per liter. The van den Bergh reaction was 2.4 mg. per 100 cc., biphasic. The urine showed + tests for albumin, diacetic acid and bile. The sediment contained occasional white cells. The sputum grew *Staphylococcus aureus*.

A roentgenogram of the chest showed a large amount of fluid in the right pleural cavity, obscuring the right diaphragm and costophrenic angle, and extending upward in the axillary line as far as the apex. Dense consolidation radiated from the hilus on each side. The left pleural cavity seemed free of fluid. There was no evidence of cavitation.

A right thoracentesis yielded 1320 cc. of thin, free-flowing, yellow, slightly turbid fluid from which *Staph. aureus* was grown. The patient's respirations at once became less labored, and his color improved, changing from blue to pink. He was given oxygen, however, and started on sulfadiazine. Several hours later, he became irrational, and required restraint. The next day, trocar thoracotomy was performed, with drainage of about 600 cc. of fluid in twenty-four hours. The patient seemed improved. A blood transfusion was given and was repeated on the fourth hospital day. At this time, there was much emphysema of the subcutaneous tissues about the trocar wound. The edema of the legs extended as high as the sacrum. The urinary output for the day was only 330 cc., with a specific gravity of 1.032 and with a ++ test for albumin. It was thought that the concentration was related to the therapy, since a sulfadiazine blood level of 10.8 mg. per 100 cc. had been attained. At this time, a roentgenogram of the chest showed numerous hazy areas of in-

creased density in the portion of the right lung that had previously been obscured by fluid.

On the sixth hospital day, a firm, slightly tender mass was palpated in the splenic area, extending two to three fingerbreadths below the costal margin, and descending with respiration. Two days later, this mass reached four fingerbreadths below the costal margin. The liver edge was not palpable. Repeated transfusions were given. The patient remained comfortable as long as he was kept in an oxygen tent. On the eighth hospital day, the temperature began to spike from 99 to 104°F. Late on the tenth day, he again became increasingly dyspneic and cyanotic. The respirations fluctuated from 50 to 60, and the pulse from 150 to 160. There was an increase in moist rales throughout both lung fields, without extension of the mediastinal shift. Tourniquets to the extremities gave no apparent relief. The patient became irrational and unmanageable. On the twelfth and last hospital day, he was quite unresponsive. After an apparent brief convulsion, he was found to have a stiff neck. The head was fixed toward the left. There was cogwheel rigidity of muscles. The eyes were held open, and the pupils were unequal, reacting sluggishly. The fundi were normal. A lumbar puncture gave clear fluid, under an initial pressure of 100 mm. of water. The fluid contained 2 or 3 lymphocytes per cubic millimeter. In the last hours, the right pupil dilated and became fixed. There were choreiform movements of the arms and legs. Respirations gradually ceased.

Differential Diagnosis

Dr. William B. Breed: I should like, first of all, to simplify this story and follow it through more or less as a straightforward acute upper respiratory infection, with purulent staphylococcal bronchopulmonary infection; and I think we can do that, particularly if we take at face value the sudden onset of disease one month prior to entry.

Apparently, the patient had an acute upper respiratory infection, with sudden onset, which progressed; he probably developed a bronchial fistula, with empyema due to *Staphylococcus aureus*. Because of this illness, he did develop some avitaminosis. The serum protein was low, perhaps because of a nutritional factor.

Certain things about this story, if one reads it over a number of times, need explaining. The first is the leukopenia found in another hospital; another is the x-ray picture, which I am not clear about and which I want cleared up. Still another is the appearance of a mass under the left costal margin in the region of the spleen, which I think we must accept as an enlarged spleen. Moreover, involvement of the central nervous system cannot be explained on the basis of acute fulminating bronchopulmonary infection alone. Before coming here, I asked one of our hematologists if, from the record, he could say that this leukopenia, which is reported with 11 per cent monocytes and a high polymorphonuclear count, indicated some underlying blood dyscrasia, such as lymphoma or aleukemic leukemia. He replied that it could represent such a condition, but that no such diagnosis could be made from the blood report alone. I agreed with that. However, I do think that we must consider the initial leukopenia with a monocytic increase as possibly being important in the fundamental diagnosis.

Now I should like to get more information on the x-ray findings.

Dr. Aubrey O. Hampton: I am afraid I am not going to give you as much information as you would like. Almost any radiologist who saw these films would first think of pulmonary edema, because any type of pneumonia that would advance to that degree is seen only post mortem. I do not believe that a patient with pneumonia, other than tuberculous pneumonia, of that extent could still be alive, particularly for so many days.

Dr. Donald S. King: The films taken in the sanatorium two weeks previously looked like that.

Dr. Breed: Did you see them?

Dr. King: Yes.

Dr. Hampton: I cannot be sure that there are abscesses in the lungs. Pulmonary edema, I think, should be ruled out because it did not change enough in the whole period of ten days. The most definite change occurred when they drained the fluid in the pleural cavity.

Dr. Breed: Do you think that the patient had pleural sepsis with bronchial fistula?

Dr. Hampton: The pleural fluid was not true pus, was it?

Dr. Champ Lyons: It was a thin fluid, which on culture gave a heavy growth of *Staph. aureus*.

Dr. Hampton: I should not expect it to have been real pus, because when it was drained the lung promptly expanded.

Dr. Breed: And there was no bronchial fistula?

Dr. Hampton: I do not believe so. I do not see any enlarged lymph nodes. In one of the films, there is a gas bubble, probably very high in the splenic flexure. I doubt very much if the spleen was enlarged. I think one would have to call this chronic bilateral pneumonia, with fluid in the right pleural space.

Dr. Breed: There are no multiple abscesses?

DR. HAMPTON: I cannot be sure. These small areas of diminished density are not clear enough for me to make a diagnosis. There is overlying air in the pleural cavity — it might be interspersed between adhesions or fibrin.

DR. BREED: It is very difficult to believe this man was entirely well a month before entry into the hospital.

DR. BREED: What was his occupation?

DR. TRACY B. MALLORY: He was a tube annealer.

DR. BREED: That does not help. I suppose a tube annealer is not a candidate for pneumoconiosis.

DR. HAMPTON: The diagnosis would have to be acute silicosis if the lesion were due to dust.

DR. BREED: I think it is obvious that this man was not completely in good health one month previous to entry, when he had a sudden onset of cough followed by nine days of sweats and chills; and I am therefore prepared to make a few conclusions about the underlying lesions. I can assure you, however, that it will be mostly guesswork because there is no accurate laboratory evidence.

DR. HAMPTON: I now have the film taken in the sanatorium a month before the one I previously demonstrated. The patient obviously had considerable pulmonary disease at that time. It started out as small and large rounded areas of density. There were some small miliary lesions.

DR. BREED: Could they be multiple staphylococcal abscesses?

DR. HAMPTON: I do not believe so.

DR. BREED: The sputum contained many staphylococci, and also the pleural fluid. Is it not so?

DR. HAMPTON: Yes.

DR. BREED: In any event, I am prepared to believe that the staphylococcal infection was not the primary cause of death. There was undoubtedly a superimposed bronchopulmonary infection due to the staphylococcus.

Nothing is stated about the cardiac situation; therefore, I must ignore it. The tourniquets put on the legs suggest some sort of cardiac failure, but I cannot be sure of that.

This question of the sudden appearance of the spleen interests me a great deal; I venture to suggest that it had been present for a long time, and that someone found it one morning.

DR. KING: It was noted in the sanatorium.

DR. BREED: I am glad to hear that because according to the record it appeared during the patient's stay in this hospital. Spleens do not appear all of a sudden. Moreover, I question whether its size really increased in two days. It certainly does not seem reasonable to believe that the spleen had increased in size in a few hours. Therefore I think this man had a chronic disease. On it was superimposed the infection that is here described.

What lead have we concerning the underlying process? If we place emphasis on the leukopenia and the spleen, we might very well consider one of the new growths of the lymphoid series, possibly lymphoma. Having thought of such a possibility, I recalled a case that was somewhat similar to this one in which during life the diagnosis was impossible, and in which the post-mortem examination showed nothing but a peribronchial infiltration by lymphomatous tissue. There were no lymph nodes, and I could never feel the spleen. Whether the patient in the case under discussion had lymphoma or aleukemic leukemia, I do not see how we can do more than guess but I do believe that he had an underlying disease a good while before the month previous to admission. The edema and the sordes and crusts on his nose are not very important except as they indicate a very sick man with malnutrition and riboflavin deficiency.

I have to conclude with the thought that the patient had a lymphoma, a lymphosarcoma or one of the lymphoid series of new growths, with, possibly, some peribronchial infiltration, and that the infection was entirely secondary. Of course, he died of the infection. He would have died of the underlying disease eventually, and it was responsible for the continuing and very bizarre pulmonary infection.

DR. KING: I think you went just far enough. You did a lot better than I thought anyone could possibly do. The patient was sent to the Middlesex County Sanatorium with the diagnosis of pulmonary tuberculosis. He ran a septic temperature, but we could find no evidence of tuberculosis. Many sputum examinations failed to show tubercle bacilli; however, the sputum did show a pure culture of *Staph. aureus*, and the blood culture showed one colony of staphylococcus. We sent the patient into this hospital, thinking that he had staphylococcal pneumonia and septicemia. After his admission here, a chest tap produced a fluid that showed staphylococcus on culture, and I believed that we were dealing with an overwhelming staphylococcal infection. But the course after that made it evident that we were dealing with some unusual condition. No one thought of lymphoma.

DR. BENJAMIN CASTLEMAN: How can you rule out carcinoma?

DR. BREED: I cannot; I forgot to mention the possibility of metastatic carcinoma, which I had considered and discarded because of the leukopenia and the splenomegaly.

DR. HAMPTON: Dr. Lingley and I have been looking at these films, and we agree that the x-ray picture at the first examination looks like that of metastatic neoplasm. I do not know the answer to this case. I noted that the first film was marked tuberculosis, and I erased it before Dr. Breed could see it. I am still going to have my say, however. Later on, the process becomes confluent, like infection, not like metastasis, and the only confluent tumor such as this that I know of is lymphoma. I am therefore inclined to agree with Dr. Breed, especially since Dr. King has complimented his diagnosis.

CLINICAL DIAGNOSES

Staphylococcal pneumonia.
Multiple liver abscesses.

DR. BREED'S DIAGNOSES

Lymphoma (? peribronchial).
Staphylococcal pneumonia, empyema and septicemia.

ANATOMICAL DIAGNOSES

Reticulum-cell sarcoma of lungs and kidney.
Multiple pulmonary infarcts.
Staphylococcal empyema.
Septic spleen.
Thrombophlebitis of femoral veins, bilateral.
Operative wound: right thoracotomy.

PATHOLOGICAL DISCUSSION

DR. MALLORY: We were startled at autopsy by the appearance of the lungs. Both lungs were virtually filled with tumor nodules running from 0.5 to 1 cm. in size. Many showed central necrosis, sometimes with dimpling of the surface, such as one sees with carcinoma. However, they were soft and in that way unlike cancer. There was very little other evidence of tumor. There were a number of slightly enlarged lymph nodes along the aorta, which, however, were not clearly neoplastic. There was, of course, the remnant of staphylococcal empyema, with thick fibrinopurulent exudate in the pleural cavity. One single metastasis about 2.5 cm. in diameter was found in the kidney.

On microscopic examination, it was immediately obvious that this was a lymphomatous tumor, and I should classify it as a reticulum-cell sarcoma. There was not very much peribronchial infiltration, but there was a good deal of perivascular infiltration, with invasion, in many places, of the arterial walls, and secondary thrombus formation.

So far as the peripheral edema of the legs was concerned, although the serum protein may have played a role, I think it was primarily due to thrombophlebitis of both femoral veins. The spleen was large but not involved by neoplasm. I should have to classify it as a septic spleen.

DR. HAMPTON: Was the intervening pulmonary tissue between the nodules normal?

DR. MALLORY: There was a great deal of tumor not all of which was limited to the sharply outlined nodules seen on gross examination. There was also vaguely outlined infarction; most of it was in tumor tissue, but some was not. This infarction, I think, was due largely to local thrombosis rather than to embolism dependent on direct invasion of the pulmonary arteries by tumor.

DR. HAMPTON: There was no edema?

DR. MALLORY: There was some, but not a great deal.

CASE 27472

PRESENTATION OF CASE

A fifty-eight-year-old housewife was admitted to the hospital for treatment of a fracture of her right thigh.

She had been seen in the hospital twelve times before, over a period of seven years, because of rheumatoid arthritis involving definitely the fingers, wrists, elbows, shoulders, feet and ankles, and involving questionably the knees, hips and spine. Following her twelfth hospital stay, her joints had appeared to improve, with some restoration of function. The only evidence of active disease was constant elevation of the sedimentation rate. The night preceding her final entry, she slipped from the edge of a bed on which she had been sitting, and fell to the floor, fracturing her right thigh above the knee.

On examination, the patient displayed the same hypertrophic changes of joints as had characterized her arthritis on earlier admissions, except for some progression of the disease in the right shoulder. There was a simple fracture of the right femur, above the knee. The heart, lungs and abdomen were essentially normal.

The temperature was 98°F., the pulse 108, and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

Examination of the blood at the time of the twelfth admission five months previously had shown a red-cell count of 4,880,000 with 16.1 gm. hemoglobin and a white-cell count of 11,400 with 74 per cent polymorphonuclears. The sedimen-

tation rate was 1.7 mm. per minute. Examination of the urine was negative.

A roentgenogram of the right thigh showed a comminuted fracture of the lower end of the femur, about 2.5 cm. above the condyles, with the fragments in excellent position.

The fracture was treated at first by suspension with traction, and later by application of a plaster cast. At the end of the seventh hospital week, the cast was removed and a splint applied to permit exercise. A roentgenogram at this time showed a small amount of callus, the fracture lines still remaining distinct. The patient received physiotherapy treatments, including the Hubbard tub, but continued to lack muscle strength. After four months, active exercise was begun.

A month later, in her thirty-fifth week in the hospital, she spent a restless night and vomited without apparent cause. The next day, she was incontinent of urine and remained in stupor, from which she could be roused. There was slight weakness of the left eyelid and left side of the face, and the tongue deviated slightly to the left. The patient was able to move all her extremities, and there was no loss of sensation. The tendon reflexes were hyperactive and equal. The plantar responses were equivocal. Speech was distinct, without aphasia or inco-ordination. The temperature, pulse and respirations remained normal. The blood pressure was 150 systolic, 95 diastolic. The next day, the patient was drowsy, but otherwise seemed normal.

Nine days after the onset of this attack, the patient again became drowsy. She had been complaining of frontal headache, "like the pressure of a telephone operator's headset." The next day, her stupor became deeper and she responded only to painful stimuli. Her lips were cyanotic, her eyelids retracted, and the right eye deviated to the left. The pupils were equal and responded to light. The fundi appeared normal. The deep reflexes were active and equal. The plantar reflexes showed withdrawal reactions. The right side of the face seemed more relaxed than the left. There were no abnormal signs in the chest or abdomen. The blood pressure was 150 systolic, 80 diastolic. During the next four days, the temperature, pulse and respirations rose gradually, reaching terminal levels of 106.4°F., 160 and 48, respectively. Death occurred at the end of the thirty-seventh hospital week, following several right-sided convulsive movements.

Differential Diagnosis

Dr. Maurice Fremont-Smith: I approach this case without my usual confidence that I have a chance of getting something right. Perhaps some of the observations were not correct; certainly, there are very large gaps in the information given us. I should like very much to throw the case open to interruptions from the floor, — especially since I see three neurologists sitting here, — because I am sure that I cannot make a very satisfactory discussion.

In the first place, the patient was admitted without apparently much the matter with her, except that she had a great deal of some sort of arthritis. She fractured her leg, was appropriately treated, and progressed satisfactorily for many weeks. Then, one night, she developed restlessness, vomiting and, the next day, stupor and cranial-nerve paralyses; she undoubtedly died from an intracerebral accident of some sort. Is there very much to help us in making a diagnosis? The patient had rheumatoid arthritis — she had been in the hospital twelve times previously, and that had been the diagnosis. On the other hand, we have the statement in the third paragraph that she displayed the same "hypertrophic changes of the joints as had characterized her arthritis on earlier admissions." That must be, I think, a misprint, or else she did have hypertrophic changes along with the underlying rheumatoid arthritis. There was not very much to indicate that the rheumatoid arthritis was still active, except the sedimentation rate, which is good evidence. It should be pointed out, however, that a sedimentation rate can sometimes get us off the track. Dr. J. Burns Amberson, Jr., yesterday at the New England Postgraduate Assembly, pointed out the difficulty in recognizing tuberculosis in the age groups from fifteen to twenty-two. Tuberculosis can go on in a few weeks to rapid involvement of the whole lung and to death, and yet in the early stages there is no cough, no temperature, no rise of pulse and no increase in sedimentation rate — nothing except films that show the disease. One cannot therefore eliminate active infection on the basis of a normal sedimentation rate. There are, moreover, and I throw this open for discussion, some older people of sixty-five or so who have high sedimentation rates — really high. I have followed several of them for years; I do not know what is causing the high sedimentation rate, which occurs without anemia and without the development of any disease. However, this patient had a high sedimentation rate, and we may accept the fact that she had active atrophic arthritis, but I cannot see any connection myself between this and her death. Perhaps there is a connection. I shall be glad to have remarks from authorities.

The only statement we have about the broken leg is that at the end of the seventh hospital week the x-ray films showed a small amount of callus and the fracture lines were distinct. I asked one of the surgical men what he would expect x-ray study to show at the end of the seventh week. He said that he would expect to see a little callus and a fracture line; consequently that is apparently normal healing of the bone. If the patient had had faulty union, one could speculate on the causes of delayed union. She had a fracture, and physiotherapy was given. The Hubbard tub, I am sure, is important, but I do not know why. Then exercises were begun, and a month later she had an episode. It seems to me that this episode, which undoubtedly was some sort of cerebral accident, was entirely independent of anything that had gone before. The patient was in the hospital and had a cerebral accident. That is all I can say. She did not have fat embolus, which comes at the time of fracture and causes collapse. That is out unless there is something abnormal about the fracture. Do we have the x-ray films?

Dr. Tracy B. Mallory: Unfortunately, they were lost.

Dr. Fremont-Smith: I was sure of it. I knew it as I read the case. If it were a pathological fracture, and if union had been delayed, and it apparently was not, I could discuss with interest the possibility of metastasis, but so far as I can see that is bringing it in by the heels. There is no reason to do so, but there is no reason to bring in anything else either. There is no focus to give emboli, no hypertension. The patient had a good blood pressure for her age. She did not have nephritis, with the possibility of injury to the blood vessels. I should like to tie up the arthritis with her death, but I do not know of any reason to connect it with a vascular accident in any part of the body or brain.

Dr. Walter Bauer: If it is of any help to you, I might add that the patient was older than the stated age.

Dr. Fremont-Smith: That does help a little bit. Something might have happened more easily.

Dr. Bauer: That she had severe rheumatoid arthritis and marked secondary degenerative joints, which developed subsequently, there can be no doubt. She was bedridden when I first saw her and had about decided to remain so the rest of her life. It was only by persuasion and the help of a good strict nurse that she was finally able to walk with a cane and lead an independent life.

Dr. Fremont-Smith: Although there is no evidence for it, when I first saw the record I thought of coronary disease because it seems to me that there is a connection between rheumatoid arthritis and disease of the coronary arteries; but that does not help explain the cerebral accident. In a woman like this it is possible that emboli arose from a vein. But one would have to assume that the embolus went through the lung, or through a patent foramen ovale, either of which is improbable. We have no evidence. The heart was normal. There is nothing to help us. All we can do is discuss the various possibilities of a lesion that would cause such symptoms as these.

I thought first of metastatic disease — I do not know from where. I thought of vascular disease, and one can also pull some other things out of the air. One could think of marked hypoglycemia, which could cause coma and evidence of organic nerve changes, such as the Babinski reflex, but would not be fatal; there is no reason, however, to consider it. One can list brain tumor or brain abscess, but there is no reason to think of one more than another, except that the patient was old and vascular injury was more likely.

Granting that something happened, where did it happen? I pause specifically for help from the neurologists. How can a lesion cause coma and involve some of the cranial nerves — therefore, probably down around the area of the pons — without involving the pyramidal tract? They are careful to tell us that there was no hemiplegia. There is no information about Babinski signs except that they were equivocal. The patient had lesions that involved first one side and then the other. She probably had multiple basal lesions on the right, but how could they be in that region without involving the pyramidal tract? She did have a convulsion at the end, which theoretically suggests subcortical irritation, but any grave cerebral accident can result in convulsions. This convulsion, however, was right-sided. One would accordingly think of something in the left subcortical region. I have not spoken about subarachnoid hemorrhage, which I think is a possibility, although we are not told whether the neck was stiff. We have little information about the headache. Again, it is very hard for me to see why there was not more involvement of the nervous system if subarachnoid hemorrhage were present. I shall say, before closing the case, that if anyone does know it would be interesting to have more comment and more speculation on the neurologic situation.

Dr. Mallory: No lumbar puncture was done,

and that puts the neurologist at a great disadvantage.

DR. FREMONT-SMITH: No harder for him than for me!

DR. BAUER: There was a very good reason for not doing a lumbar puncture. This patient was between sixty-five and seventy years of age, rather than fifty-eight. We were quite certain that she was going to die. Furthermore, we knew that a post-mortem examination would be granted and that the cause of the cerebral symptoms would probably be ascertained at that time. Therefore, I did not think it necessary to do a lumbar puncture. Perhaps it should have been done for the benefit of this conference.

A PHYSICIAN: Would Dr. Fremont-Smith think of multiple lesions as a cause of the vagueness of signs?

DR. FREMONT-SMITH: I think that there must have been more than one lesion, and I should like a little comment from someone.

DR. MALLORY: Your preference is for a vascular lesion?

DR. FREMONT-SMITH: I should think so in a woman of this age.

DR. BAUER: What type of lesion?

DR. FREMONT-SMITH: I do not know.

DR. CHARLES S. KUBIK: There was drooping of the left upper eyelid. There was no difference in the size of the pupils.

DR. MALLORY: I should be inclined to vote against a vascular lesion. The patient had a very gradual deepening of symptoms, whereas most vascular lesions come on suddenly and then tend to improve. This showed the reverse.

DR. JAMES B. AYER: There is no explanation for the fever except on a neurologic basis?

DR. BAUER: No; not that we could find. It is only fair to say that the lungs were not examined posteriorly the last day or two.

DR. AYER: This case does not conform to vascular thrombosis; we lack the signs of bilateral cortical deficiency from thrombosis on both sides of the brain; and also we fail to have the findings of basilar-artery thrombosis.

Attention to the Hubbard tub is probably due to the fact that the hospital has recently acquired this useful article.

DR. BAUER: Since the patient had rheumatoid arthritis involving the right knee and a fracture of the right thigh, the treatment of which required a long period of immobilization, fibrous-tissue ankylosis occurred. I hated to think that this needed to be permanent. Therefore, she was treated in the Hubbard tub, in the hope that we could prevent complete loss of motion of the right knee.

DR. MALLORY: Do you want to go ahead and tell us more about it?

DR. BAUER: We proceeded along much the same line of reasoning as Dr. Fremont-Smith did. Because of the sudden onset of headache, I first considered a subdural hematoma. As I saw the patient subsequently, I wondered if she might have multiple cerebral thromboses, a diagnosis that was not confirmed. I have forgotten what my final diagnosis was. I can assure you I was not certain of the exact cause of death.

A PHYSICIAN: Was the convulsion one sided?

DR. BAUER: I do not know. I did not see her at the time it occurred.

DR. MALLORY: The diagnosis was cerebral thrombosis.

CLINICAL DIAGNOSIS

Cerebral thrombosis.

DR. FREMONT-SMITH'S DIAGNOSIS

Cerebral lesions due to vascular injury.

ANATOMICAL DIAGNOSES

Subdural hematoma, left, cerebral.
Rheumatoid arthritis, chronic.
Operative scars: left coracoid osteotomy; cholecystostomy; cholecystectomy; and appendectomy.
Fracture of right femur, old.
Peritonitis, healed, fibrous.
Pleuritis, healed apical, left.
Pulmonary edema, moderate.
Arteriosclerosis: coronary, moderate; aortic, minimal.
Leiomyoma uteri, with calcification.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At post-mortem examination, the significant findings were in the brain. There was, of course, generalized rheumatoid arthritis and a moderate amount of arteriosclerosis of the aorta and a slight amount of the coronary arteries, but nothing that should have functionally impaired the heart.

Dr. Kubik will tell us the interesting points in the brain.

DR. KUBIK: The finding of drooping of the left upper lid was probably significant. One might have expected an inequality of the pupils and dilatation of the left pupil as well. The lesion was a subdural hematoma on the left side, a fairly large one, surrounded by a rather thin membrane. It did not look as if it were old, and I should not

suppose that it resulted from the fall out of bed several months before death. I do not believe we have any indication of why this occurred. There was characteristic flattening of the frontal lobe by the hematoma, and slight displacement of the midline structures to the opposite side. There was actually some herniation of the medial surface of the hemisphere beneath the falx, a good deal of herniation of the cerebellum into the foramen magnum and slight herniation of the hippocampal gyri into the notch of the tentorium.

DR. FREMONT-SMITH: Should not the disks have been choked?

DR. KUBIK: They usually are not with subdural hematoma, and I should not expect them to be in a case of short duration.

DR. FREMONT-SMITH: Is not a spontaneous affair much more likely to be subarachnoid than subdural?

DR. KUBIK: Yes.

DR. BAUER: The patient had no stiffness of the neck. One would expect a higher temperature with a subarachnoid hemorrhage. These and other findings kept us from making this diagnosis.

DR. MALLORY: Can you see anything in retrospect that should have made one more suspicious of subdural hemorrhage?

DR. KUBIK: No; I do not.

DR. BAUER: After seeing the autopsy, I thought it was much more likely a spontaneous hemorrhage.

DR. KUBIK: I do not believe that it could have been due to the injury nine weeks before.

DR. BAUER: I think it is fair to say that the patient was not quite herself after the accident. She had nausea, vomiting and drowsiness, but there was no mention of headache.

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The Journal does not hold itself responsible for statements made by any contributor.

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ACCURATE BOOKKEEPING RECORDS OF HUMANITY

The Bureau of the Census refers to the vital statistics of births and deaths as "accurate bookkeeping records of humanity," and the term is not overdramatized since on these data are based such figures as life-expectancy tables, population estimates, information on migration and fertility, and public-health trends. The chief responsibility for accurate records rests on physicians, since 90 per cent of the births and deaths in the United States are attended by them. The officials charged with recording these data find it necessary each week to return many certificates, particularly those reporting deaths, because of the inaccuracy and vague phraseology employed.

A uniform vital-statistics act was recommended to the several states in 1939, but there is no guarantee that it will be adopted without change. Some form of registration procedure is required in every state, but the provisions vary to an amazing extent. Maine, in 1821, was the first state to pass legislation requiring registration, and Massachusetts followed in 1840; and complete records for births and deaths since 1848 are available in New Jersey.

The Department of Commerce, through the Bureau of the Census, publishes a pamphlet* which contains the "International List of Causes of Death" and the additional information that every physician needs to know before he can execute a certificate correctly. Much of the confusion and discussion occurring in medicolegal situations could be decreased or eliminated if this or a similar reference were consulted and used. This is particularly true of those who are removed in point of time or distance from centers of medical education, the physicians in contact with hospitals and teaching services being more meticulous in their use of medical terminology.

The changing nature of our social concepts requires more frequent reference to birth and death certificates, and the physician has a dual obligation — to give more thought to the law and to his patient or the family, particularly to the latter. If he has familiarized himself with the case, he need not find difficulty in being specific. The certificate is of a confidential nature, and no physician should hesitate to indicate a disease such as chronic alcoholism if he is convinced that it is the principal cause of death. The contributory causes — those "which contribute to the risk of dying" — apply to minor underlying or accompanying conditions, including the use of alcohol and drugs. If there is doubt in the physician's mind about the actual role of any factor, a discussion of the case with the proper medicolegal officer may save much embarrassment and time for himself, the relatives and, in certain cases, the courts. If general terms must be used, they should be accompanied and linked with an

**Physicians' Handbook on Birth and Death Registration.* 94 pp. Washington, D. C.: Government Printing Office, 1939. This can be obtained from the Superintendent of Documents, Washington, D. C., at a cost of 15 cents.

anatomic site. Medical terms which include the names of men should be avoided. Thus, exophthalmic goiter is preferable to Basedow's or Graves's disease.

The registration of vital statistics is maintained by city, state and federal agencies at considerable expense, and as a matter of economy alone, the basic material should be as carefully presented to the officials charged with registration as is a prescription to an apothecary.

GRANTS FOR THE STUDY OF POLIOMYELITIS

THE National Foundation for Infantile Paralysis has awarded new grants totaling $195,030 for research on the etiology, treatment and prevention of poliomyelitis, it was recently announced by Basil O'Connor, president of the foundation.

The objects of the foundation — the control and eventual eradication of the disease and the proper care of those afflicted — can be attained only by study of the virus, the exact nature of which is still unknown, of the most effective therapy and of the character and amelioration of the permanent consequences.

Of the twenty-eight grants made to achieve these purposes, three are of particular interest to physicians in Massachusetts. Two awards totaling $6300 have been bestowed on the Children's Hospital in Boston to continue the study of the effects of infantile paralysis on the lower extremities and to inaugurate research to determine the effects of prolonged bed rest and other factors in the development of calculi or stones in the urinary tracts of patients with the disease. The Massachusetts General Hospital has received $2500 to continue the study of clinical cases of infantile paralysis in which the patients have an unequal growth of the lower extremities. A study of the gastrointestinal tract as the portal of entry of the virus has been made possible by a grant of $3000 to the Boston City Hospital.

The splendid work of the National Foundation for Infantile Paralysis merits the support of the medical profession and the laity. The courage and zeal of the foundation in carrying on its relentless fight against a dreaded disease are an inspiration and a challenge to those who struggle against other diseases that threaten life and health.

MEDICAL EPONYM

LANE'S KINK

W. Arbuthnot Lane (b. 1856), surgeon to Guy's Hospital, London, first described this condition in an article, entitled "Chronic Constipation: A consideration of its surgical treatment," which appeared in *Surgery, Gynecology and Obstetrics* (**6**: 115–129, 1908).

> . . . . There can be no doubt that the pathological changes which are present in these conditions of imperfect drainage are most obvious and important. . . . The portion of the caecum above the brim of the pelvis, together with the ascending colon, is retained in a position of abnormal fixity to the posterior wall of the abdomen. This is affected [*sic*] by the development of adhesions between the outer aspect of the large bowel and the peritoneum covering the abdominal wall in its vicinity. . . . As a rule these adhesions merely fix the bowel, but occasionally they constrict its lumen very materially in one or more situations and render it liable to become obstructed. Not only do the adhesions anchor this part of the large bowel, but they also bind down to the iliac fossa a proportion of the appendix. . . . The result of this arrangement is that, when the caecum is loaded, it exerts a vertical strain upon the proximal portion of the appendix and causes that structure to become flexed abruptly at the lower limit of its adhesions. . . . When I recognise that the mechanics of the intestines have been altered to a degree that cannot be rectified satisfactorily by the division of bands, etc., I divide the ileum at a distance of about five or six inches from the caecum, . . . the descending colon and sigmoid are removed, the rectum . . . being occluded in the same manner as the ileum.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

SPONTANEOUS, INCOMPLETE ABORTION, FOLLOWED BY FATAL HEMORRHAGE

A twenty-eight-year-old para II was not seen until she was referred to the hospital by a physician who had been called by the patient because she was flowing.

The past history was irrelevant. Physical examination on admission was normal. The patient

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section. Letters should be addressed to Dr. Raymond S. Titus, *Secretary*, 330 Dartmouth Street, Boston.

was about three months pregnant, and was bleeding very freely. The pulse ranged from 120 to 140, and she was in some degree of shock.

The first step in treatment was a transfusion of 600 cc. of citrated blood. Then, the patient was examined vaginally. The placenta, which was found lying in the cervix, was removed, and the uterus packed. Since the patient continued to bleed, the pack was removed, and the uterus examined for retained pieces of tissue; none were found. In spite of the transfusion and stimulants, the patient died.

Comment. This is a case of spontaneous incomplete abortion associated with fatal hemorrhage. Massive hemorrhage from abortion is rarely seen before the twelfth week. Not infrequently, however, a patient with an incomplete abortion may start bleeding at six or eight weeks and continue to bleed freely off and on, which eventually results in a hemoglobin below 50 per cent and a correspondingly low red-cell count; such patients seldom bleed to the point of exsanguination.

Since it is reported that there were no products of conception left in the uterus in this case, the absence of contractility of the uterus must have been due to the lack of muscular tone that is associated with the shock that accompanies so many of these large hemorrhages. Everything possible seems to have been done for this patient. The record does not say that the patient had been bleeding off and on before the hemorrhage was alarming enough to cause her to seek medical advice. If this had occurred and if the patient had been under medical observation, with no attempt to investigate the cause of bleeding, the medical attendant might well have been criticized.

DEATH

STOODLEY — HARRY M. STOODLEY, M.D., of Somerville, died November 5. He was in his sixty-fourth year.

Born in Charlestown, Dr. Stoodley received his degree from Tufts College Medical School in 1904. He was a former member of the Massachusetts Medical Society.

He is survived by his widow, two sons and a sister.

CORRESPONDENCE

NURSE-MIDWIVES

To the Editor: I was greatly interested in your editorial in the August 21 issue of the *Journal*, entitled "Maternal Welfare and the National Emergency," in which the use of the trained nurse-midwife in solving some of our problems of maternal care is suggested.

The Community Health Association, as you know, is the visiting nurse association for the City of Boston — a private agency dependent largely on the Greater Boston Community Fund for its support. In our nursing program, care of maternity patients is one of the biggest services. Last year, for instance, over 8000 prenatal cases in the city were registered with us for nursing care and supervision. This includes care during the prenatal period, assisting the physician at the time of delivery if the mother is delivered at home, and care to mother and baby during the post-partum period. If the mother is delivered in the hospital, the nurse makes one or two visits after she returns home with her baby, to demonstrate the baby's bath and instruct the mother.

While the majority of maternity patients in Boston are delivered in hospitals at the present time, there are still a goodly number who remain at home under the care of a private physician or of one of the out-door delivery services conducted by the teaching hospitals. It is the policy of our association to give nursing supervision to prenatal cases only when they are registered with a physician or clinic, and we have always had excellent working relations with both private physicians and clinics.

In spite of this seemingly adequate maternity program in the City of Boston, we realize that there are still many maternity patients who go without prenatal supervision and only seek medical care when labor starts. Our nurses are constantly on the alert in their general nursing program to find these patients and to urge them to get under medical care. Even so, there are many that elude us.

Do you feel that there is a place in Boston for the nurse-midwife? Should we be urging some of our well-prepared nurses to secure this training and go into this field of service?

DOROTHY J. CARTER, *General Director*
Community Health Association
Boston

* * *

No one will deny that the care of maternity cases, particularly in Boston, owing in part to the efforts of the Community Health Association, has been markedly bettered in the last ten or fifteen years. The fact remains, however, as brought out in the editorial and acknowledged by Miss Carter, that many cases do not receive proper, if any, attention. Furthermore, in the event of mobilization, it is obvious that even more mothers would receive inadequate medical care. The editorial suggested that the possibility of utilizing, with rigid supervision, the trained nurse-midwife in crowded tenement districts and in sparsely settled rural communities — a practice now prohibited by Massachusetts statutes — be given due consideration. ED.

PREMARITAL MEDICAL EXAMINATIONS

To the Editor: The Massachusetts premarital health-examination law has been amended so that physicians on active service in the armed forces of the United States may make the required examination.

For this purpose the Department of Public Health has approved all serologic laboratories of the United States Army, Navy and Public Health Service and all laboratories operated by state health departments and by the District of Columbia. All other physicians practicing in Massachusetts must send the blood specimen for serologic examination for syphilis to an approved laboratory in Massachusetts.

A further amendment requires that the department furnish blank forms of certificates required under the act to city and town clerks.

PAUL J. JAKMAUH, M.D.
State House *Commissioner of Public Health*
Boston

BOOK REVIEWS

Biological Symposia. Vol. I. *The Cell Theory; Mating Types and Their Interactions in the Ciliate Infusoria; Chromosome Structure.* Edited by Jaques Cattell. With a foreword by Albert F. Blakeslee, Ph.D. 4°, cloth, 238 pp., with 39 illustrations and 19 tables. Lancaster, Pennsylvania: The Jaques Cattell Press, 1940. $2.50.

The Jaques Cattell Press is to be congratulated in making permanent the biological symposiums held at the Richmond meeting of the American Association for the Advancement of Science. These symposiums present the latest authoritative information in the various fields of biology. A good idea of the subject matter covered may best be obtained by listing the subjects discussed and the experts who participated in them.

The first symposium was on the cell theory; Dr. Joseph Mayer was chairman. The papers presented were: "The Cell Theory: Its past, present and future," by Dr. Joseph Mayer; "Microscopy before the Nineteenth Century," by Professor Lorande L. Woodruff; "Schleiden's Contribution to the Cell Theory," by Professor John S. Karling; "Predecessors of Schleiden and Schwann," by Professor Edwin G. Conklin; "A Modern Concept of the Cell as a Structural Unit," by Professor George A. Baitsell; "The Present Status of Mitosis," by Professor Franz Schrader; "The Problem of Cell Individuality in Development," by Professor Paul Weiss; "What of the Future?" by Professor Clarence E. McClung.

The second symposium was on mating types and their interactions in the ciliate infusoria; Dr. Herbert S. Jennings was chairman. After an introduction by Dr. Jennings, the topics considered were: "*Paramecium aurelia,*" by Dr. Tracy M. Sonneborn; "*Paramecium bursaria,*" by Dr. Jennings; "Studies on Conjugation in *Paramecium multimicronucleatum,*" by Professor Arthur G. Giese; "Mating Types in *Paramecium caudatum,*" by Lauren C. Gilman; "Mating Types in Euplotes," by Richard F. Kimball.

The third symposium was on chromosome structure, with Professor Theophilus S. Painter as chairman. The topics considered were: "On Coiling in Chromosomes," by Dr. Bernhard R. Nebel; "The Physicochemical Nature of the Chromosome and the Gene," by Dr. C. H. Waddington; "The Structure of Salivary Gland Chromosomes," by Professor Painter; "Chromosome Structure as Viewed by a Geneticist," by Dr. Millislav Demerec.

Biological Symposia. Vol. II. *Speciation; Defense Mechanisms in Plants and Animals; Biological Basis of Social Problems; Regeneration.* Edited by Jaques Cattell. With a foreword by George A. Baitsell, Ph.D. 8°, cloth, 270 pp., with 13 illustrations and 1 table. Lancaster, Pennsylvania: The Jaques Cattell Press, 1941. $2.50.

The second volume on biological symposiums will excite the interest of all students concerned with the phenomena of life.

The topics dealt with in the first symposium were: "Introduction," by Dr. Leon J. Cole; "Speciation of Fishes," by Dr. Carl L. Hubbs; "Ecologic and Genetic Variability within Species of Peromyscus," by Dr. Lee R. Dice; "Speciation from the Point of View of Genetics," by Dr. M. R. Irwin and Dr. R. W. Cumley; "Breeding Structures of Populations in Relation to Speciation," by Professor Sewall Wright; "Speciation Phenomena in Birds," by Dr. Ernst Mayr; "Speciation in Peromyscus," by Dr. Lee R. Dice; "Levels of Divergence in Drosophila Speciation," by Professor Warren P. Spencer; "Speciation as a Stage in Evolutionary Divergence," by Professor Theodosius Dobzhansky.

The second symposium, on the topic of defense mechanisms in plants and animals, comprised: "Local Reactions in Plants," by Dr. Fritz W. Went; "Generalized Defense Reactions in Plants," by Dr. W. C. Price; "Local and Generalized Defense Reactions in Animals," by Dr. William Bloom.

The third symposium, on the biological basis of social problems, was composed of the following: "Introduction," by Dr. Samuel J. Holmes; "A Few Words About Nature," by Dr. William E. Ritter; "Social Integration as a Biological Process," by Professor Charles M. Child; "The Naturalist as a Social Phenomenon," by Dr. Francis B. Sumner; "The Ethics of Enmity in Social Evolution," by Professor Holmes; "A Biologist's Appreciation of Religion as a Factor in Social Evolution," by Dr. Edwin B. Copeland.

The fourth symposium, concerning regeneration, contained the following papers: "Introduction," by Professor J. William Buchanan; "The Histologic Basis of Regeneration and Reassociation in Lower Invertebrates," by Dr. Winterton C. Curtis; "The Environmental Control of Regeneration in Euplanaria," by Dr. Olin Rulon; "Aspects of Regeneration in Annelids," by Dr. Libbie H. Hyman; "Contributions to the Problem of Regeneration in Protozoa," by Dr. William Balamuth.

NOTICES

MASSACHUSETTS GENERAL HOSPITAL

A meeting of the Hospital Research Council will be held in the Bigelow Amphitheater of the White Building on Tuesday, November 25, at 5 p.m.

PROGRAM

Effect of the Serum of Patients with Graves's Disease, Myxedema and Acromegaly on the Oxygen Consumption of Guinea-Pig Thyroid. Dr. Carlos Galli-Mainini.

Chemotherapy of Experimental Staphyloccal Infections. Dr. Champ Lyons.

Retardation of Epiphyseal Growth by Roentgen Irradiation. Drs. J. S. Barr, E. A. Gall and J. R. Lingley.

Further Studies on the Optimal Solution for the Dissolution of Calcium Phosphate Calculi. Drs. Fuller Albright, R. Murdoch, H. Suby and H. Sulkowitch.

JEWISH MEMORIAL HOSPITAL

A diagnostic and therapeutic conference will be held at the Jewish Memorial Hospital on Thursday, November 27, at 11 a.m. Dr. J. H. Swartz will speak on "Diseases of the Skin."

Physicians and medical students are invited to attend.

NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society will be held at the Peter Bent Brigham Hospital on Thursday, November 27, at 8 p.m. Dr. William Dock, professor of pathology at Cornell University Medical College, will speak on "The Kidney and Hypertension."

Physicians and medical students are cordially invited.

(Continued on page xii)